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THE SIGNIFICANCE OF THE BACTERIA FOUND IN THE THROATS OF HEALTHY PEOPLE

By Arthur L. Bloomfield

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In studying the etiology and pathogenesis of infectious diseases the problem is simplified vastly by the existence of a lesion from which the virus may be recovered in pure culture. Meningitis and sepsis, conditions which previously were but incompletely understood, immediately became intelligible from the bacteriological standpoint following the introduction of spinal puncture and blood cultures which made it possible to study the organisms derived in pure culture from the seat of the disease. The causal agents of respiratory disease, on the other hand, have proven much more elusive, and the proof of their relation to particular lesions is much more difficult, since the ground is already occupied by organisms not primarily causing the process, or at least is open to secondary invasion from the upper air passages by a host of unessential organisms. It required several years to establish the pneumococcus as the cause of lobar pneumonia, and a generation later we find the problem of the etiology of influenza even more perplexing and thus far insoluble. In reviewing the history of the latter disease it becomes apparent that confusion has arisen through the focussing of the investigator's attention upon one or another organism without due consideration of the flora as a whole both in health and in disease.

During the course of studies on the fate of bacteria introduced into the upper air passages it became apparent that foreign organisms were rapidly eliminated. It seemed probable, therefore, that the true normal flora of these regions might be relatively simple and constant, and that, if it could be clearly defined, a background would be obtained against which the flora present in various disease conditions might reasonably be contrasted with less chance of misinterpretation. For example, should it turn out that the green streptococcus is constantly present in normal throats, its presence in disease would have to be interpreted with great caution, whereas an organism not normally present in healthy throats, if persistently found in a given individual, would indicate disease or at least an abnormal carrier state. It immediately became clear that a large number of single cultures from various individuals would help but little in the solution of this problem. The literature already affords ample information as to the great variety of organisms which may be recovered from the apparently normal throat. Thus, it appeared more hopeful to study the flora of a few individuals repeatedly at frequent intervals over a considerable period of time, as by this means one could determine not only the organisms present, but their persistence as well as their relative predominance. Moreover, chance temporary invaders could be distinguished from bacteria actually dwelling in the mouth cavity.

Methods

Six healthy individuals were selected for study. They included the physicians and personnel working in the bacteriological laboratory, and being constantly and intimately exposed to infectious diseases of all sorts. In addition, a few patients not suffering from disease of the respiratory tract were investigated. Cultures were made about once a week from each of these individuals over a period of from one to three months. A swab was systematically passed over the tonsils, pillars, soft palate, and posterior pharyngeal wall and immediately plated. Aërobic methods only were used. The media consisted of plates of 5 per cent blood agar (human or rabbit) and of Avery's oleate hemoglobin medium. Four plates were made from each swab, a system of dilutions being employed which yielded a good spread of colonies on the plates. Cultures as ordinarily made, resulting in a confluent growth, are useless in this sort of work. The plates were studied after 24 and after 48 hours from two points of view. First a careful search was made for the presence of *B influenzæ, Strept. hemolyticus,* the meningococcus, pneumococcus and staphylococcus albus and aureus. Then a study was made of the other organisms present. Every type of colony present was fished and the numbers of each estimated as accurately as possible. The cultures were worked out in great detail, about four hours being found necessary for the complete study of one set of plates.

Results

It soon became apparent that certain organisms were almost constantly present from day to day. Before analyzing the results in detail a few general remarks may be made about each of the groups of organisms present.

(1) *The Gram-Negative Cocci.*—In practically every plate the predominating organisms were found to belong to the group of Gram-negative cocci. At first an attempt was made to differentiate several varieties and strains on the basis of colony size and consistency, pigmentation, and growth on various media. This task was soon abandoned as impossible, inasmuch as every variation was found, from small translucent grey colonies to large, dry crinkly pigmented ones. Finally, the study of this group was confined to the elimination of the meningococcus, the remaining organisms being classed simply as Gram-negative cocci. As one becomes familiar with the appearance of plates made by a constant method, the colonies of these bacteria stand out as a characteristic background. With the exception of a few cases which will be discussed in connection with the protocols they were present in every culture and undoubtedly are a constant and normal inhabitant of the upper air passages.

(2) *The Non-Hemolytic Streptococci.*—These organisms as well as the Gram-negative cocci were present in nearly every culture. Undoubtedly many strains exist—as evidenced by variation in appearance of the colonies, and in the morphology of the organisms. The usual type is a small grey semi-transparent colony 0.5 to 1 mm. in diameter with a slight greenish zone of clearing; microscopically, the bacteria are usually in long chains and show considerable pleomorphism. Organisms belonging to this group are undoubtedly constant inhabitants of the normal throat, although temporarily they may be replaced by other bacteria.

(3) *Influenza Bacilli.*—Members of the group of hemophilic Gram-negative bacilli were found in most of the cultures. The position of this organism is still in doubt, and inasmuch as these studies were made at a time when respiratory disease was prevalent one hesitates to draw final conclusions. A special study of this problem is now in progress. It may be said, however, that Gram-negative hemophiles may be present in large numbers in the throats of healthy people constantly and over considerable periods of time.

The above three groups seem to comprise very definitely the constant normal flora of the mouth when cultures are made by this method. We are inclined to believe that the presence of any other organism demands a special explanation—either the presence of disease, a focus of latent infection, or accidental introduction. Before presenting the protocols a few general remarks may be made about the other organisms considered in this study.

Hemolytic streptococci of the typical beta type were not obtained in any case. This is of interest, as the cultures were made from people who were in intimate contact with patients suffering from sore throats due to these organisms. We believe that their presence in normal throats, as reported by some writers, indicates the recent presence of widespread infection among large groups of people with a virulent type of the germ. Hemolytic streptococci of the alpha type were occasionally found but never as constant inhabitants. Their significance will be discussed in connection with the individual cases.

Pneumococci were occasionally found. Inasmuch as mouse inoculation was not employed, their presence may have been overlooked in some cases. All suspicious colonies were carefully studied, however, and this organism is certainly not a member of the normal flora in the strict sense.

Meningococcus was found in no instance. This was to be expected as there was no meningitis in the environment at the time.

Staphylococci were found occasionally, but never constantly, in the same normal throat. This organism, therefore, when present, is an accidentally introduced transient unless associated with a local infection.

Diphtheroid bacilli, Gram-positive cocci of various sorts, and other organisms, as described in the protocols, are not uncommonly present, but only as transients.

The non-pathogens in the throat may, therefore, be divided into the members of the constant normal flora—Gram-negative cocci, non-hemolytic streptococci, Gram-negative hemophiles (?)—and a group of organisms commonly present about the body such as staphylococci, diphtheroids, and others, which not infrequently may be introduced into the mouth but are transients and are promptly eliminated.

Protocols

A scrutiny of the protocols herewith presented will bring out more clearly the points discussed above.

CASE I.—MO

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Mar. 13..	∞ *	A few.	0	0	0	0	0	A Gram-pos. diphtheroid, 20 cols.
" 23..	100	Many.	0	Type IV, a few cols.	A few.	0	0	
" 31..	Many.	Many.	0	Type IV, a few cols.	∞	0	0	
Apr. 6..	∞	∞	0	0	Many.	0	0	
" 21..	Many.	∞	0	0	0	∞	0	
" 26..	∞	∞	0	0	Many.	0	0	

Comment.—The non-hemolytic streptococci and Gram-negative cocci were constantly present. Influenza bacilli were recovered in four of six cultures. A Type IV pneumococcus was temporarily present, and on one occasion Staph. albus was recovered. A diphtheroid was present in the first culture, but was never isolated again.

In this case, therefore, we have the constant normal flora, with the occasional transient presence of other non-pathogenic organisms.

* ∞ = innumerable.

CASE II.—CA

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Feb. 24..	200	∞	0	0	200	0	0	A large Gram-pos. coccus, 200 cols.
" 27..	Few.	∞	0	0	300	0	0	A large Gram-pos. coccus, a few cols.
Mar. 3..	10	∞	0	0	A few.	0	0	A yeast, 1 col.
" 10..	∞	Many.	0	0	A few.	0	0	
" 17..	∞	∞	Many cols. alpha type	0	A few.	0	0	
" 24..	∞	∞	0	0	100	0	0	

Comment.—The non-hemolytic streptococci, the Gram-negative cocci and influenza bacilli are constantly present. An alpha type hemolytic streptococcus was recovered in one culture, but not before or after. A large Gram-positive coccus was present for a few days and then disappeared. We have, therefore, in this case the normal flora plus the transient presence of other organisms.

CASE III.—BL

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Mar. 4..	∞	∞	Alpha type 100 cols.	0	A few.	0	0	A Gram-pos. diphtheroid, many cols.
" 8..	A few.	∞	0	0	100	0	0	
" 24..	∞	∞	0	0	Many.	0	0	
Apr. 1..	∞	∞	0	0	Many.	0	0	A Gram-pos. diphtheroid, many cols.
" 8..	∞	∞	0	0	Many.	0	0	Many cols. of a Gram-neg. hemolytic bacillus.
" 26..	Many.	Many.	Alpha type a few cols.	0	Many.	0	0	

Comment.—Non-hemolytic streptococci, Gram-negative cocci, and influenza bacilli were constantly present. Alpha hemolytic streptococcus was present as a transient on two occasions, as well as a gram-positive diphtheroid and a Gram-negative hemolytic bacillus. The significance of the hemolytic streptococcus is uncertain. It may have been harbored in the tonsil whence it was discharged from time to time.

CASE IV.—V

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Feb. 28..	∞	80	0	0	∞	0	0	
Mar. 1..	∞	∞	0	0	Many.	1	0	
" 3..	∞	Many.	0	0	100	0	0	1 col. hemolytic staph. Many cols. Gram-pos. diphtheroid. 100 cols. coarse Gram-pos. coccus.
" 6..	Many.	∞	0	0	Many.	0	0	Many cols. Gram-pos. diphtheroid.
" 9..	∞	Many.	0	0	50	0	0	∞ cols. Gram-pos. diphtheroid.

Comment.—Non-hemolytic streptococci, Gram-negative cocci, and influenza bacilli were constantly present. From time to time various other organisms were isolated, especially a Gram-positive diphtheroid.

CASE V.—AL

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Jan. 3..	∞	∞	0	0	A few.	Many.	0	Gram-pos. diphtheroid many cols.
Feb. 23..	∞	Several hundred.	0	0	Several hundred.	0	0	Gram-pos. diphtheroid many cols.
" 26..	∞	∞	0	0	∞	0	0	
" 28..	∞	∞	0	0	Many.	0	0	

Comment.—Non-hemolytic streptococci, Gram-negative bacilli, and influenza bacilli were constantly present. Staph. albus was isolated on one occasion, and a Gram-positive diphtheroid twice.

CASE VI.—CA

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Feb. 24..	200	∞	0	0	200	0	0	Huge Gram-pos. coccus, 200 cols.
" 27..	A few.	∞	0	0	Several hundred.	0	0	A few of the above.
Mar. 3..	10	∞	0	0	A few.	0	0	A yeast, one col.
" 10..	∞	∞	0	0	0	0	0	
" 17..	∞	∞	Alpha type many.	0	A few.	0	0	
" 25..	∞	∞	0	0	Many.	0	0	

CASE VII.—BV

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Feb. 22..	Many.	∞	0	0	∞	0	0	Gram-pos.diphtheroid, 20 cols.
" 25..	∞	∞	0	0	∞	0	0	
" 29..	∞	∞	0	0	∞	0	0	A pigmented staph., 20 cols.
Mar. 2..	∞	∞	0	0	Many.	0	0	A large Gram-pos. coccus, 50 cols.

CASE VIII.—MA

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Mar. 10..	∞	∞	0	0	A few.	3	0	
" 29..	∞	∞	0	0	Many.	150	0	
April 7..	∞	∞	0	0	A few.	2	0	
" 27..	∞	∞	0	0	Many.	0	0	A Gram-pos. coccus, not S. albus, many cols.
" 30..	Many.	∞	0	0	Many.	0	0	About 50 cols. of a minute Gram-pos. organism (?).

Comment.—The normal flora is present. In addition Staph. albus was recovered in small numbers in three consecutive cultures, after which it disappeared.

CASE IX.—ER

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Mar. 4..	∞	∞	0	0	0	0	0	
" 9..	∞	50	0	0	0	0	0	A Gram-pos. diphtheroid, many cols.
" 16..	∞	∞	Alpha type many cols.	Type IV many cols.	0	0	0	A coarse Gram-pos. coccus, many cols.
" 25..	∞	∞	Alpha type many cols.	0	100	0	0	
Apr. 5..	∞	∞	0	0	A few.	0	0	
" 13..	∞	∞	0	0	0	0	0	Sev. hundred colonies of a Gram-neg. bacillus, large grey cols. with hemolysis.
" 16..	50	Many.	0	0	0	0	0	Many cols. of a coarse Gram-pos. coccus, not S. albus.
" 20..	∞	∞	0	0	Many.	3	0	50 cols. of same Gram-neg. bacillus as found in culture of Apr. 13.
" 25..	∞	∞	0	0	Many.	0	0	

Comment.—The normal flora is present. In addition, influenza bacilli and other bacteria were transiently present. A mild pharyngitis lasting two days preceded the appearance of the alpha hemolytic streptococcus recovered on March 16 and March 25.

CASE X.—GI

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Mar. 1..	∞	0	0	0	0	0	0	∞ Friedländer.
" 5..	Many.	A few.	0	0	0	0	0	∞ Friedländer. ∞ Gram-pos.diphtheroid. 50 cols. of a coarse Gram-pos. coccus.
" 12..	∞	A few.	Alpha type many.	0	0	0	0	∞ Friedländer.
" 17..	∞	A few.	0	0	0	0	0	∞ Friedländer.

Comment.—This patient was a carrier of the Friedländer bacillus, which tended to supplant the normal flora.

CASE XI.—DO

Date of culture	Non-hemolytic streptococcus	Gram-negative cocci	Hemolytic streptococcus	Pneumococcus	Influenza bacillus	Staph. albus	Meningococcus	Remarks
Mar. 12..	Many.	20	0	0	3	∞	0	
" 15..	0	100	0	Type II many?	0	∞	0	
" 20..	∞	∞	0	0	0	50	0	A yeast, 50 cols.
" 27..	Many.	∞	Alpha type many.	0	Many.	100	0	
Apr. 2..	Few.	Few.	0	0	Few.	∞	0	
" 12..	Many.	∞	0	0	0	50	0	
" 22..	∞	∞	0	0	0	20	0	Many cols. of a Gram-pos. coccus—not Staph. albus.
Nov. 4..	∞	∞	0	0	A few.	0	0	

Comment.—This person was affected with a subacute rhinitis and pharyngitis following an acute cold. In the first culture the normal flora was practically replaced by a white staphylococcus. As this organism decreased in numbers, the normal flora reappeared in the usual proportions.

Discussion

It appears that cultures made repeatedly from the throat of the healthy individual over a considerable length of time reveal two groups of organisms. In the first place there is a group—non-hemolytic streptococci, and Gram-negative cocci—which is constantly present and seems to constitute the true normal flora of the throat in the sense of actually living its complete life history in that environment. In addition to this group many other organisms may be recovered in cultures from normal throats but their presence seems to be only transient. They disappear within a few days, as a rule, just as foreign organisms do when experimentally introduced. It is possible that some of these organisms such as pneumococci and influenza bacilli are really constant inhabitants, but are present in such small numbers that they were missed in some of the cultures, but this seems unlikely. We may picture, therefore, in addition to the true basic flora a constant influx of various bacteria from the skin, the nose, the air, and from external objects.

These, unless they are pathogenic and set up disease, seem to be promptly disposed of by the normal protective mechanism of the upper air passages (chiefly mechanical flushing.) The idea, then, that bacteria in general, when introduced into the upper air passages are likely to colonize and live there indefinitely is erroneous. It is now clear, both from these studies and from the experimental work, that the normal surfaces of the upper air passages afford a very unfavorable environment for foreign organisms, both pathogenic and non-pathogenic, and that special conditions are needed to make possible their prolonged or permanent presence.[2] Such conditions as a rule consist of the production of disease, or at least a focus of diseased tissue in which the organisms may colonize.

With these points clearly in mind it seems that one is in a much better position to study the bacteriology of infections of the upper respiratory tract. Knowing the normal flora, and the possibility of transient invaders, unessential organisms may be readily discounted. A study of the bacteriology of colds is now being taken up from this point of view.

Conclusions

I. The organisms present in the throats of healthy people, as revealed by this method, fall into two groups:

(a) The true normal flora including non-hemolytic streptococci and Gram-negative cocci, and

(b) Pathogenic or non-pathogenic organisms which are accidentally introduced and are present usually only a short time in a given individual.

II. A true picture of the normal flora is obtained only by making repeated cultures from the same individual.

REFERENCE

1. Bloomfield, A. L.: American Review of Tuberculosis, 1920, IV, p. 247.

EXPERIMENTAL INOCULATION OF HUMAN THROATS WITH AVIRULENT DIPHTHERIA BACILLI

By W. L. Moss, C. G. Guthrie and B. C. Marshall

(From the Division of Clinical Pathology of the Medical Clinic, The Johns Hopkins University and Hospital)

For a proper appreciation of the relation of the healthy diphtheria bacillus carrier to the community it would be helpful to know which persons are actually carriers or at least the approximate proportion of carriers in the population at large. Next it obviously would be of practical importance to ascertain whether any cases of clinical diphtheria develop among the associates of these carriers.

In a previous communication on this subject[1] we have reported that a single examination of a large series of individuals (2507), both children and adults, in the winter and spring of 1911, revealed an incidence of healthy diphtheria bacillus carriers of about 3.55 per cent. It was also found that a second examination of a large series of persons practically doubled the number of carriers discovered, while a third examination still further increased the original number. It should be pointed out that the percentage of carriers probably varies in different localities in the same year or in the same locality in different years. We found that in the same locality it also varied considerably with the time of the year, being somewhat higher during the winter than in the summer months. Making all allowance for such variation, however, there still exists a number of diphtheria carriers so great as to be out of all proportion to the number of clinical instances of the disease.

With regard to the second point, namely, the relation of these carriers to the occurrence of clinical diphtheria in the community, we were quite unable to discover any instances of the disease among the associates of the carriers studied by us. One hundred and sixty additional carriers were studied the following year (1912) and during the three and a half months covered by our observations no cases of diphtheria were found among their associates.[2]

Investigation also showed that of the total number of healthy carriers under observation—over 200 in all—only 11 per cent (1912) to 18 per cent (1911) harbored virulent diphtheria bacilli. Even 11 to 18 per cent of the total, however, constitutes a number of carriers disproportionately large when compared with the reported incidence of the disease. Despite the fact that we were unable to incriminate any of the carriers under observation in the actual spread of diphtheria, it was recognized, nevertheless, that those who harbored virulent organisms constitute a potential menace to the community.

With regard to the healthy carriers of non-virulent diphtheria bacilli, however, the condition is quite different. Here we have no evidence whatever that any danger exists as a result of the carrier state and on this point we have expressed our conviction strongly.

Two questions are raised from time to time which have a distinct bearing upon the validity of our conclusions concerning the harmless nature of the healthy carrier of non-virulent diphtheria bacilli. The first question concerns the reliability of the guinea-pig test for toxin production by the diphtheria bacillus, with the suggestion that an organism which is non-virulent for the guinea-pig may be in reality virulent for man. The second question is based upon the assumption that a non-virulent strain of *B. diphtheriæ* from the throat of a healthy carrier may become virulent on longer residence in the throat

[1] Moss, W. L., Guthrie, C. G., and Gelien, J.: Diphtheria Bacillus Carriers. Trans. XV Internat. Cong. on Hyg. & Dem., 1912, IV, 156.

[2] Guthrie, C. G., Gelien, J., and Moss, W. L.: Diphtheria Bacillus Carriers, Second Communication. Johns Hopkins Hosp. Bull., 1920, XXXI, 388.

of that carrier, or may acquire virulence when introduced into the throat of another individual. It was to put these and certain other questions to experimental test that the present work was undertaken.

In another place[3] were reported the results of animal experiments designed to show whether the previous injection of diphtheria antitoxin had any effect in preventing the lodgment and growth of diphtheria bacilli, either virulent or non-virulent. Among the facts which seemed apparent from this work were the following:

(1) The production of nasal infection or infestation of cats, rabbits and guinea-pigs with *B. diphtheriæ* was quite inconstant even when the organisms were introduced directly into the nose.

(2) The duration of infection was usually quite short but may have been variable in this respect, as some of the animals still harbored diphtheria organisms at the end of the experiments.

(3) The occurrence and duration of infection were independent of the virulence of the strain of organism used for inoculation and (4) were wholly unaffected by the previous administration of antitoxin.

It was found that certain conditions in these experiments with animals were quite different from those which obtain with human beings; notably that in a considerable series of animals (112) none was found spontaneously infected with diphtheria bacilli and that the carrier state was difficult to induce. Feeling, therefore, that the results of this work might not be entirely applicable to man, further experiments were carried out, this time with human beings instead of animals as subjects.

OBJECT

1. To determine whether the introduction of avirulent diphtheria bacilli into the throats of healthy human beings will result in the production of the carrier state and, if produced, how long it may last.

2. To determine whether the lodgment and growth of the bacilli may be prevented by the previous injection of diphtheria antitoxin.

3. To determine whether the organisms introduced are capable of producing (a) clinical diphtheria; (b) any subjective symptoms; (c) any objective signs in the appearance of the throat.

4. To determine whether any cases of clinical diphtheria develop among the associates of artificially produced "healthy carriers"[4] of virulent diphtheria bacilli.

5. To determine whether the organisms introduced into the throats of normal human beings are in any way changed by this procedure, particularly as to (a) morphology; (b) staining characteristics; (c) cultural characteristics; (d) ability to produce toxin (virulence).

PROCEDURE

Five physicians (W. L. M., C. G. G., S. R. M., A. W. S. and W. A. B.) volunteered to be subjects of these experiments. These individuals, designated for the sake of brevity in the following pages as *A*, *B*, *C*, *D* and *E*—were healthy men varying in age from 28 to 36 years. Only one had had clinical diphtheria and only one had previously received antitoxin; *D* had had a severe attack at the age of five, before the introduction of diphtheria antitoxin; *E* had received a prophylactic injection of antitoxin in 1911. Only one of the five has had diphtheria or received antitoxin since the close of these experiments; *B* had a definite attack the following year (1914) as the result of experimental inoculation with virulent organisms obtained from the throat of a healthy carrier; at this time he received three injections of antitoxin.

Preliminary throat cultures on these five persons were made daily over a period of two weeks to ascertain whether any had diphtheria bacilli in their throats at the beginning of the experiments.

At the end of this preliminary fortnight three members of the group (*C*, *D* and *E*) received a subcutaneous injection of 250 units of diphtheria antitoxin before being inoculated with the non-virulent diphtheria bacilli. The two remaining members of the group (*A* and *B*) received no antitoxin.

The strain of diphtheria bacillus employed in this work (Culture 48) was obtained by us from a healthy carrier during an investigation of public school children in 1912 and at the time of the experiments reported in the present paper (1913) it had been growing on Loeffler's blood serum for 12 months. When first isolated the strain proved to be non-virulent; repeated tests over a period of a year—15 or more, including those made just at the beginning of this work—in each instance confirmed the original result. Morphologically, tinctorially and culturally the strain was typical *B. diphtheriæ* and was indistinguishable from our virulent strains except by the animal tests for the production of toxin.[5]

The inoculations were made from transplants of this strain grown on Loeffler's blood serum for 24 hours and then suspended in normal salt solution. By using the growth from several tubes, this saline suspension was rendered quite thick and almost milky in appearance.

The inoculations were made by soaking a cotton throat swab in the bacterial suspension and then rubbing it over both tonsils and the posterior pharyngeal wall. As none of the five individuals yielded positive cultures on the following day, a second inoculation was made two days after the first. For this purpose a freshly prepared bacterial suspension was used similar in all respects to the other. This time, however, the suspension was placed in an atomizer and with this the throats of the five individuals were thoroughly sprayed.

[3] Gelien, J., Moss, W. L., and Guthrie, C. G.: The Effect of Diphtheria Antitoxin in Preventing the Lodgment and Growth of the Diphtheria Bacillus in the Nasal Passages of Animals, Johns Hopkins Hosp. Bull., 1920, XXXI, 381.

[4] The term "healthy carrier" is used in distinction to "convalescent" or "contact" carrier.

[5] For further details concerning the methods employed in the identification of this and other strains of *B. diphtheriæ* see reference cited above, "Diphtheria Bacillus Carriers, Second Communication."

Daily cultures were made from four members of the group (*A, B, C* and *E*) from February 4, 1913, to May 28 of the same year, a period of 114 days or a little over 16 weeks, and then at intervals until July 9, a period of six weeks more. From the other member (*D*) daily cultures were made from February 4, when the experiment began, until he left on an expedition to South America on April 28. Beginning the next autumn, occasional cultures were made from each member of the group until January 12, 1914, when daily cultures were begun again and continued for several months.

The results of the cultures taken from February 4 to July 9, 1913, are shown in the accompanying chronological table (Table I). The blanks in the earlier part of the table indicate days on which members of the group were absent from the laboratory. The table has been condensed from the 120th day onward by omitting the days on which no cultures were taken. In this table a *positive* culture is indicated by +; a *negative* culture by 0; A. T. indicates a subcutaneous injection of diphtheria antitoxin; Inoc. indicates inoculation of the throat with avirulent diphtheria bacilli.

TABLE I

Day	Date	A	B	C	D	E	Day	Date	A	B	C	D	E
1	Feb. 4	0	0	0	0	0	62	April 6	..	..	..	..	..
2	" 5	0	0	0	0	0	63	" 7	..	+	+	+	+
3	" 6	0	0	0	0	0	64	" 8	..	0	+	+	+
4	" 7	0	0	0	0	0	65	" 9	..	0	+	+	+
5	" 8	0	0	0	0	0	66	" 10	..	0	+	+	+
6	" 9	..	..	..	..	..	67	" 11	..	0	+	+	0
7	" 10	0	0	0	0	0	68	" 12	..	0	+	+	+
8	" 11	0	0	0	0	0	69	" 13	..	..	..	..	..
9	" 12	0	0	0	0	0	70	" 14	..	0	+	..	+
10	" 13	0	0	0	0	..	71	" 15	..	0	+	..	+
11	" 14	0	0	0	0	0	72	" 16	..	..	..	..	..
12	" 15	0	0	0	..	..	73	" 17	+	+	+	..	+
13	" 16	..	0	..	..	..	74	" 18	..	0	+	..	+
				A. T.	A. T.	A. T.	75	" 19	..	..	..	..	..
14	" 17	0	0	0	0	0	76	" 20	..	..	..	..	..
		Inoc.	Inoc.	Inoc.	Inoc.	Inoc.	77	" 21	..	0	+	+	+
15	" 18	0	0	0	0	0	78	" 22	0	0	..	+	+
16	" 19	0	+	0	+	..	79	" 23	0	0	+	+	+
		Inoc.	Inoc.	Inoc.	Inoc.		80	" 24	0	0	+	+	+
17	" 20	0	+	+	+	0	81	" 25	..	..	..	..	..
						Inoc.	82	" 26	..	..	..	..	..
18	" 21	0	+	+	+	0	83	" 27	..	..	..	+	..
19	" 22	+	+	+	+	..	84	" 28	0	..	..	+	+
20	" 23	6	+	..	..	+	85	" 29	..	..	..	..	..
21	" 24	0	+	+	+	0	86	" 30	..	0	+	..	..
22	" 25	+	+	+	+	+	87	May 1	0	0	..	..	+
23	" 26	0	+	+	+	+	88	" 2	..	..	..	..	..
24	" 27	0	+	+	+	+	89	" 3	..	..	..	..	..
25	" 28	+	+	+	+	+	90	" 4	..	..	..	..	..
26	Mar. 1	0	+	+	+	+	91	" 5	..	0	+	..	+
27	" 2	+	+	..	+	+	92	" 6	..	+	+	..	..
28	" 3	+	+	+	+	+	93	" 7	..	..	..	..	..
29	" 4	..	..	..	..	..	94	" 8	+	0	+	..	0
30	" 5	+	+	+	+	+	95	" 9	0	0	+	..	+
31	" 6	+	+	+	+	+	96	" 10	..	0	+	..	0
32	" 7	+	+	+	+	+	97	" 11	..	..	..	..	..
33	" 8	+	+	+	+	+	98	" 12	0	0	+	..	0
34	" 9	+	+	..	+	+	99	" 13	+	0	+	..	0
35	" 10	+	+	+	+	+	100	" 14	..	0	..	..	+
36	" 11	+	+	+	+	+	101	" 15	+	0	+	..	+
37	" 12	+	+	+	+	+	102	" 16	..	0	..	..	+
38	" 13	+	+	+	+	+	103	" 17	..	0	+	..	+
39	" 14	+	+	+	+	+	104	" 18	..	0	..	..	0
40	" 15	+	+	+	+	+	105	" 19	..	0	..	..	+
41	" 16	+	+	..	+	+	106	" 20	0	0	+	..	+
42	" 17	+	+	+	+	+	107	" 21	..	..	..	..	..
43	" 18	+	+	+	+	+	108	" 22	0	0	+	..	..
44	" 19	+	+	+	+	+	109	" 23	+	..	..	..	+
45	" 20	+	+	..	+	+	110	" 24	0	..	..	..	+
46	" 21	0	0	..	+	+	111	" 25	..	..	..	..	..
47	" 22	+	0	..	+	+	112	" 26	..	0	+	..	..
48	" 23	0	+	..	..	+	113	" 27	0	0	+	..	+
49	" 24	0	0	+	+	+	114	" 28	..	0	+	..	..
50	" 25	0	+	..	+	+	115	" 29	..	..	..	..	..
51	" 26	+	+	..	+	+	116	" 30	..	..	..	..	..
52	" 27	0	0	+	+	+	117	" 31	..	..	..	..	..
53	" 28	0	0	+	+	+	118	June 1	..	..	..	..	..
54	" 29	0	0	+	+	+	119	" 2	..	0	+	..	+
55	" 30	+	0	..	..	+	120	" 3	..	..	..	..	..
56	" 31	+	+	+	+	+	134	" 17	0	0	+	..	+
57	April 1	+	+	+	+	+	143	" 26	0	0	+	..	+
58	" 2	+	0	+	+	+	144	" 27	..	0	+	..	+
59	" 3	..	+	+	+	+	148	July 1	0	0	+	..	0
60	" 4	..	+	+	..	+	149	" 2	..	..	..	..	..
61	" 5	..	0	+	..	+	156	" 9	..	0	0	..	0

From Table I it will be seen that the preliminary cultures taken daily over a period of two weeks (from February 4 to February 17 inclusive) were negative. We therefore felt that the five individuals who had volunteered for these experiments were not already carriers of diphtheria bacilli.

On February 17, three members of the group (*C*, *D* and *E*) received 250 units of diphtheria antitoxin subcutaneously. Six hours later these three together with the other two members (*A* and *B*), who had received no antitoxin, were inoculated by swabbing the throats with a saline suspension of avirulent diphtheria bacilli, as described above. Cultures taken on the day following this inoculation proved to be negative in each case, but owing to the time necessary for incubation, the result of these cultures was not known until the day after they were taken, that is, the second day after inoculation of the throats. The negative results having led us to suppose that the inoculation had been ineffective, we reinoculated the entire group by spraying a thick suspension of bacilli into the throat with an atomizer as previously described. Cultures made on the second day after the first inoculation and just before the second inoculation were positive in the cases of two members of the group (*B* and *D*) and it seems not unlikely that the first inoculation alone would have sufficed to establish the carrier state in all five members of the group. Following the second inoculation, the cultures of *B*, *C* and *D* were regularly positive for many days.

In the case of *A*, the first positive culture did not appear until three days after the second inoculation and regularly positive cultures were not established until eleven days after the second inoculation.

In the case of *E*, the first positive culture was obtained three days after the second inoculation. This was succeeded by one negative culture, after which the cultures became regularly positive.

It is seen, therefore, that as the result of experimental inoculation with avirulent diphtheria bacilli the carrier state was established in all five members of the group, in those who had received a previous inoculation with diphtheria antitoxin (*C*, *D* and *E*) and in those who had not (*A* and *B*).

The results obtained from the beginning of the experiment on February 4, 1913, to the end of the first series of observations on July 9 of the same year may be summarized from Table I.

From Table II it is seen that the apparent duration of the carrier state as determined by these observations was as follows: *A*, 91 days; *B*, 77 days; *C*, 132 days; *D*, 39 days; and *E*, 125 days. For *A* and *B* this probably represents approximately the actual duration of the carrier state, as cultures from their throats were continued for from six (*A*) to nine weeks (*B*) after the last positive result had been obtained and no further positive cultures were found either during this period or on examination made subsequently to the present series. *D* was a carrier from February 19 until April 28, the date on which he left Baltimore. That he probably remained a carrier for a long time thereafter was shown by the result of cultures taken upon his return in the succeeding fall. *A* and *E* continued to yield positive cultures practically to the end of the first series of observations, recorded in Table I. The last positive culture from *C* was obtained on July 1, followed by one negative on July 9; from *E* the last positive culture was obtained on June 27, followed by negatives on July 1 and 9. That both of them were carriers for a very long time was shown by the result of cultures taken at intervals during the fall of 1913 when those from *E* were occasionally and those from *C* regularly positive.

As mentioned before, daily cultures on the entire group were begun again on January 12, 1914, and continued until May 29 of the same year. In this series *D* showed only one positive culture—that taken on January 17—whereas the cultures from *C* and *E* were frequently positive up to the very end of this series of observations. With regard, then, to the duration of the carrier state as judged from the combined observations extending over 15 months—(February 4, 1913, to May 29, 1914)—it may be said that in *A* it was 91 days, in *B* 77 days, in *D* 11 months, while *C* and *E* were still carriers at the end of 15 months.

TABLE II

Cultures	A	B	C	D	E
Total	74	99	81	64	92
Preliminary	12	13	12	11	10
After 1st inoculation with *B. diphtheriæ*.	62	86	69	53	82
After 1st inoculation, before 1st positive.	4	1	3	1	3
After 2d inoculation with *B. diphtheriæ*.	60	84	67	51	80
After 2d inoculation, before 1st positive.	2	0	0	0	1
Date of 1st positive	2–22–13	2–19–13	2–20–15	2–19–13	2–23–13
Date of last positive	5–23–13	5–6–13	7–1–13	4–28–13	6–27–13
Date of last culture	7–1–13	7–9–13	7–9–13	4–28–13	7–9–13
Total positive	32	39	66	52	70
Total cultures after and including 1st positive.	58	85	67	52	79
Per cent positive cultures after 1st inoculation.	51.61%	45.34%	95.65%	98.11%	85.36%
Per cent positive cultures after and including 1st positive.	55.17%	45.88%	98.50%	100%	88.60%

It is obvious that the previous administration of 250 units of diphtheria antitoxin did not prevent the lodgment and growth of the non-virulent diphtheria bacilli in the throats of *C*, *D* and *E*. Indeed, the actual number of positive cultures obtained from them in the first series of observations was much greater (*C*, 66, *D*, 52, *E*, 70) than from *A* and *B*, who had received no antitoxin (*A*, 32, *B*, 39). The same point is emphasized when we compare the percentage of positive cultures (*C*, 95.65%, *D*, 98.11%, *E*, 85.36%; *A*, 51.61%, *B*, 45.34%). The duration of the carrier state also was markedly less in *A* and *B* who did not have antitoxin (*A*, 91 days, *B*, 77 days) than in *C*, *D* and *E* who received it (*D*, 11 months, *C* and *E*,

15 months plus). We do not wish to imply, however, that the previous administration of antitoxin renders an individual more liable to become a carrier when inoculated with avirulent diphtheria bacilli or that it is responsible for a prolongation of the carrier state when thus induced, but merely to emphasize the fact that in our experiments antitoxin did not prevent the development of the carrier state nor shorten its duration.

Throughout our observations an effort was made to indicate in a general way the relative numbers of the diphtheria organisms seen in the stained preparations from the positive cultures. This was carried out in our records of all but 12 of the 259 positive cultures encountered up to July 9, 1913, by the use of a rough, comparative scale, as follows: (1) Only one or two diphtheria bacilli seen. (2) Very scanty. (3) Scanty. (4) Moderate number. (5) Numerous. (6) Very numerous. (7) Almost pure culture. These comparative figures are omitted in Table I since they distract attention from the much more important point as to whether a given culture is positive or negative and might be interpreted as implying much more than we feel they deserve or intend to suggest. A study of these records, however, revealed certain points of interest, confirming general impressions which we had gained from previous studies of carriers. When the carrier state was once firmly established and the cultures were regularly positive each day, the organisms were recovered in great abundance. Before the carrier state was firmly established, as evidenced by occasional negative cultures, the organisms were recovered in fewer numbers. After what might be called the height of the carrier state and when occasional negative cultures were obtained, there were great fluctuations in the number of organisms recovered. Finally, it appeared that before the organisms disappeared entirely from the throat they became scanty, were consequently much less apt to be recovered and considerable intervals elapsed between the positive cultures.

When we come to consider the effect of the inoculation with avirulent organisms on the health of these five men, we are at once confronted by the question whether any of them possessed natural immunity against diphtheria toxin and so may have escaped harmful effect, not because the organisms were harmless, but because of efficient protection. This question is, of course, of much less importance in so far as it concerns *C*, *D* and *E* who were passively immunized by the injection of antitoxin than it is with regard to *A* and *B* who received no such injection. Although it had been known for some time that certain persons had a natural immunity against diphtheria toxin due to the presence of circulating antitoxin in the blood, the methods of testing for this natural immunity were so tedious as to render their application infrequent. It was not until the introduction of a more simplified method by Schick that large series of persons were tested and some knowledge was obtained as to the comparative frequency of natural immunity to diphtheria toxin. The preliminary report of the work done by Schick appeared in 1908 and this was followed by other reports from time to time.[6] Our attention was not directed to his work, however, until the publication of his papers in 1913, some time after the beginning of these experiments; consequently skin tests were not made on the five volunteers to determine the presence or absence of natural immunity prior to inoculation. Tests performed on them some months later, however, showed that four (*A*, *C*, *D* and *E*) had some amount of circulating antitoxin in the blood, whereas *B* on numerous occasions showed a complete absence of antitoxin as indicated by a strongly positive test at each trial. This lack of natural immunity in *B* was later confirmed by the fact that he developed a frank attack of diphtheria the following year (1914) as the result of experimental inoculation with virulent diphtheria bacilli.

It is the opinion of those with wide experience in the use of the Schick reaction that when natural immunity against diphtheria toxin, as manifested by a negative skin test, is once developed in persons beyond the age of five or six years, this immunity is probably life long.[7] If this impression is correct we may infer that *B* was without natural immunity to diph-

[6] Schick, B.: Kutanreaktion bei Impfung mit Diphtherietoxin. Vorläufige Mittheilung, München. med. Wchnschr., 1908, LV, 504. *Also*, Ueber Diphtheriekutanreaktion. Verhandl. d. Gesellsch. f. Kinderh., Köln, 1908, XXV, 330.

Schick and Novotny, J.: Ueber Diphtheriekutanreaktion beim Meerschweinchen. Ztschr. f. Immunitätsforsch. u. exper. Therap., 1910, Th. 1, Orig., IV, 550.

Schick and Michiels, Jules: Die intrakutanreaktion des Menschen auf Diphtherietoxininjektion als Ausdruck des Schutzkörpergehaltes seines Serums. Festschrift für Kassowitz, Julius Springer, Berlin, 1912, p. 232.

Schick and Magyar, Fritz: Versuche mit intrakutaner Injektion von Diphtherietoxin beim Menschen. Verhandl. d. Gesellsch. f. Kinderh., Münster, 1912, XXIX, 9.

Schick: Spezifische Therapie der Diphtherie. Centralbl. f. Bakteriol., 1913, Div. I, Ref., Suppl., LVII, 16.

Schick and Michiels, Jules: Ueber die Wertbestimmung des Schutzkörpergehaltes menschlichen Serums durch intrakutaner Injektion von Diphtherietoxin beim Menschen. Ztschr. f. Kinderh., 1913, Orig., V, 349.

Schick: Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjektion. München. med. Wchnschr., 1913, LX, 2608.

[7] Personal communication from Dr. W. H. Park, Director of the Research Laboratory of the Department of Health, New York City: "As a general statement one can say that a child developing antitoxin and therefore giving a negative Schick test will remain negative for life. We have, however, followed children in institutions from year to year and found that each year about 2 per cent of those who have given negative tests changed to positive. There is undoubtedly some fluctuation from time to time in the amount of circulating antitoxin and also some difference in the toxin dilution employed for the test in the different years, so that I am not quite sure how much to ascribe to the change in the child, and how much to the technique of the injector and the strength of the toxin used. This is equally true for those who have developed a negative Schick test after artificial immunization by means of toxin-antitoxin injections, as indicated by the results of our observations extending over five years. It should be mentioned, however, that some of these apparent changes from a condition of immunity to one of susceptibility are possibly to be explained by mistakes in the records resulting from the fact that two or more children may bear the same name, thus rendering it difficult to avoid confusion."

theria toxin at the beginning of our work, but although we cannot state with certainty that *B* had no protection and that *A*, *C*, *D* and *E* had circulating antitoxin and therefore natural immunity against diphtheria toxin at the time these experiments were begun, we know that this was the case when tested some months later, at a time when all the passive immunity conferred by the antitoxin injected in *C*, *D* and *E* would have long since disappeared. We do not know when any of these persons developed their immunity. In the case of *D*, we know that he was not immune at the age of five, for at that time he had a severe attack of diphtheria. Moreover, just as we cannot say positively that *A*, *C*, *D* and *E* were not immune at the time these experiments were begun, so we are unable to say whether any of them developed their immunity as a result of the experimental inoculation with avirulent diphtheria bacilli. That it did not have this effect in the case of *B*, however, has been indicated. The selection of *C*, *D* and *E* as control individuals to receive antitoxin, all of whom were immune when tested some months later and who probably had homemade antitoxin circulating in their blood at the time our experiments were begun, was entirely due to chance. That *B*, the only individual in the group who was presumably without natural protection, was chosen as one of the two without artificial protection, was chance also.

The clinical effect of experimental inoculation with non-virulent diphtheria bacilli could, of course, be judged only on the two individuals—*A* and *B*—who did not receive a preliminary injection of antitoxin. Of these, *A* had antitoxin present in his blood when tested at a later date—quite possibly this was present before our experiments began—thus leaving only *B* without natural or artificial protection. That *B* was later susceptible to the effect of diphtheria toxin has been pointed out; that he was susceptible, at the time of our work, to whatever ill effect these non-virulent organisms were capable of producing, is most probable.

Viewed in retrospect two shortcomings are quite apparent in the plan of our experiments. First, only individuals without natural immunity should have been selected for this work, certainly for that portion of the group which was not to receive passive immunization; second, there should have been a larger series of these individuals without natural or passive protection, from which to draw conclusions. Bearing in mind these limitations, such facts as we have are presented.

Careful observation of the five persons forming this group failed to reveal any untoward effect resulting from the carrier state thus artificially established by the inoculation of non-virulent diphtheria bacilli into their throats. More specifically, (1) none of them developed clinical diphtheria; (2) none had any subjective symptoms such as sore throat except when due to the attempts at eradication of the bacilli to be described shortly; (3) none showed any objective signs such as redness of the throat, pharyngitis or tonsillitis except when due to the cause just mentioned.

The daily life of these five persons was not restricted in any way. No one outside of the laboratory knew them to be diphtheria bacillus carriers. No cases of clinical diphtheria developed among their associates.

To determine whether any change had taken place in the bacilli as the result of their residence in the human throat, the organisms were isolated at intervals from the positive cultures obtained from these five individuals and tested culturally, tinctorially and by guinea-pig inoculation. Morphologically the organisms were unchanged and their staining characteristics were the same as before they were introduced into the throat. On cultural tests, also, no difference was observed in the character of the growth on Loeffler's blood serum, plain agar or in bouillon, while the changes in litmus milk and in the tests for fermentation of the various sugars were the same as with the original organisms.

Each time an isolation was made the pure culture was tested for virulence. None of the cultures so tested killed a guinea-pig or even rendered one ill. Thus it will be seen that after months of residence in the human throat (15 months in the case of *C* and *E*) there was no evidence of acquisition of virulence.

The question may be raised as to how we know that the organisms harbored by these carriers and recovered by us from time to time were of the same strain that we originally put into the throats. We do not know that they were, but there were certain facts which made us feel relatively sure on this point. In the first place none of the subjects of these experiments were carriers at the time the bacilli were placed in their throats but all of them became carriers shortly thereafter, so shortly as to leave little doubt concerning the relation of the artificial inoculation to the positive cultures obtained from the five individuals. In the second place, the carrier state, once established, lasted for a long time in all—longer in some than in others—but from each individual regularly positive cultures were obtained over a considerable period. These positive cultures, for the most part, showed not one or two organisms to a slide but myriads, indicating that the diphtheria bacilli were not merely persisting but actually multiplying in the throats. Thirdly, the identity of the strain of organisms recovered from the throats with that originally introduced was strongly suggested by the results of the tests applied to the pure cultures isolated at intervals from each of the individuals in the series. The agreement with the original strain was so definite as to render it highly improbable that these five persons had all gotten rid of the original strain and had all picked up another exactly like it.

A very definite carrier state having been established in all five of the subjects of these experiments, an attempt was made to eradicate the bacilli from the throats of *A* and *B*. The work of Churchman[8] has shown the very definite inhibitory action exerted by Gentian Violet on the growth of many of the Gram-positive organisms *in vitro*, among others *B. diphtheriæ*, and this we have confirmed with the strain (No. 48) used in these experiments and with many other strains, virulent and non-

[8] Churchman, J. W.: The Selective Bactericidal Action of Gentian Violet, Jour. Exp. Med., 1912, XVI, 221.

virulent. Accordingly we endeavored to ascertain the effect *in vivo* of this dye upon *B. diphtheriæ*. An aqueous solution of Gentian Violet was prepared in dilution of 1 to 1000 and with this the nose and throat of *A* and *B* were thoroughly sprayed on the evening of March 13, 1913. Within an hour there developed in both individuals the symptoms of an acute coryza. The mucous membrane of nose and throat became congested and there was experienced the raw, burning sensation which characterizes an inflammation of these surfaces. Headache and pain behind the eyes followed and the backache and joint pains of grippe were present. This condition gradually wore off but persisted in less pronounced degree for several days, thus discouraging the further use of an aqueous solution of the dye in a strength of 1 to 1000. The cultures from *A* and *B*, moreover, continued regularly positive. Three days later, after a partial recovery from the discomfort of the first application of Gentian Violet, the treatment was resumed, a more dilute solution, 1 to 3000, however, being employed. The nose and throat were sprayed night and morning for two days with a return of the same unpleasant symptoms which had followed its first use. Two days later (March 31) positive cultures were obtained from both *A* and *B;* in the succeeding eight days, six positive and three negative cultures were obtained. The cultures from *C, D* and *E,* who had not been treated with Gentian Violet, remained regularly positive.

At this time we made a dilution of the dye in normal salt solution in 1 to 10,000 strength and began using it daily on all members of the group, spraying the nose and throat just after the daily culture; this was continued for about ten days. After the inauguration of this treatment:

(1) *A* had eight positive cultures (March 31; April 1, 2 and 17; May 8, 13, 15 and 23) and 14 negative cultures (April 22, 23, 24 and 28; May 1, 9, 12, 20, 22, 24 and 27; June 17 and 26; July 1).

(2) *B* had seven positive cultures (March 31; April 1, 3, 4, 7 and 17; May 6) and 39 negative cultures, 17 prior to his last positive on May 6 and 22 from this date to the time of the end of the series of observations on July 9.

(3) *C* continued regularly positive until after July 1.

(4) *D* continued regularly positive until after April 28, at which time he left the city.

(5) *E* continued regularly positive, with the exception of one negative culture obtained on April 11, until after May 5. The majority of his cultures after this date were positive but from time to time a negative culture was obtained (14 positive and 7 negative from May 5 to July 9).

The results obtained on cultures of these individuals in the succeeding fall, winter and spring will be recalled; *C, D* and *E* continued to be carriers for many months; *A* and *B* did not.

Although the figures might seem to indicate that the Gentian Violet may have had some effect in eradicating the bacilli from the throats of *A* and *B*, the discomfort arising from the use of the more concentrated solutions was so great that the procedure could hardly become popular. It is, moreover, quite possible that the apparent disappearance of the bacilli at about this time was spontaneous and merely coincident with the use of Gentian Violet. It should be pointed out, also, that while occasional negative cultures were first obtained from both *A* and *B* following the employment of Gentian Violet, positive cultures from each of them were encountered at intervals thereafter over a long period (71 days in the case of *A;* 54 days in the case of *B*).

There was no evidence that the use of 1 to 10,000 dilution of Gentian Violet sprayed into the throat once daily had any effect in causing the disappearance of diphtheria bacilli from the throats of carriers.

The two chief difficulties in the use of Gentian Violet for this purposes are (1) its irritating effect upon the mucous membranes and (2) its lack of penetration, the latter, perhaps, depending to a certain extent upon the former. When applied to the throat, there is produced almost at once an abundant secretion of mucus which intervenes between the tissues and the dye, lifting the latter from the surface and preventing penetration.[9]

From the results of some subsequent work—to be reported in another paper—concerning the actual location of the diphtheria bacilli in the throats of carriers, we should not expect that the eradication of these organisms could be accomplished by the use of Gentian Violet or any other substance introduced into the throat by means of swabs, sprays or gargles.

With regard to the symptoms experienced by *A* and *B* following the use of too concentrated solutions of Gentian Violet we feel very definitely that these were not caused by the diphtheria bacilli in the throat. The 1 to 1000 and 1 to 3000 solutions were very irritating and the irritating effect was experienced right after the application and did not recur except when a strong solution was again employed as a spray. The diphtheria bacilli, it is true, were present in the throat at the time, but they had been there from three to four weeks before any symptoms developed and remained for six to ten weeks after the symptoms subsided without causing any difficulty whatever, either objective or subjective.[10] *C, D* and *E,* who had no applications of the stronger solutions, the use of which was followed by unpleasant results in *A* and *B*, had neither symptoms nor local signs in the throat although they were carriers for many months.

[9] That similar observations have been made by others is seen from the following quotation concerning the treatment of a diphtheria carrier with Gentian Violet. "The results were somewhat suggestive but an unexpected obstacle was met in the secretion of the mucous glands of the pharynx in a thin slimy layer, which was renewed by fresh secretion as rapidly as it was removed and which prevented intimate contact between dye and mucous membrane as effectually as a layer of grease would have done." Churchman, J. W., and Herz, L. F.: The Toxicity of Gentian Violet and its Fate in the Animal Body. Jour. Exp. Med., 1913, XVIII, 579.

[10] Other conceivable but improbable explanations of the symptoms produced by the stronger solutions of Gentian Violet might be mentioned:

(1) Destruction of some of the avirulent diphtheria bacilli by the Gentian Violet, with the liberation of an endotoxin capable of producing the symptoms. (2) Disturbance in a balanced, antagonistic flora produced by Gentian Violet, with production of symptoms by the unopposed group.

SUMMARY

From the results of the experiments herein reported certain facts seem sufficiently important to warrant repetition for the sake of emphasis.

(1) The carrier state was easily produced in human beings by inoculation of the throat with avirulent diphtheria bacilli.

(2) When thus produced the carrier state lasted for a long time; two of the carriers still harbored avirulent diphtheria bacilli after 15 months.

(3) The previous administration of diphtheria antitoxin subcutaneously did not prevent the lodgment and growth of the organisms.

(4) Inoculation of avirulent diphtheria bacilli into the throats of human beings did not produce: (a) clinical diphtheria; (b) any subjective symptoms; (c) any objective change in the appearance of the throat.

(5) The results of the guinea-pig test for virulence were confirmed when thus tested with human beings.

(6) No cases of clinical diphtheria developed among the associates of these artificially produced "healthy carriers" of avirulent diphtheria bacilli.

(7) When isolated in pure culture after prolonged sojourn in the human throat, the bacilli were not altered in morphology or in their staining or cultural characteristics.

(8) The bacilli showed no tendency to become virulent as a result of this type of animal passage, either in the carriers who had received diphtheria antitoxin or in those who had not.

(9) Spraying the nose and throat with Gentian Violet in a strength which could be tolerated seemed to be without effect in eradicating avirulent diphtheria bacilli.

The results of this experimental inoculation of the throats of human beings with avirulent diphtheria bacilli are in entire accord with those obtained in our previous work with healthy diphtheria bacillus carriers. The same general conclusions drawn from our earlier work have merely been confirmed and somewhat amplified.

CONCLUSIONS

1. Avirulent diphtheria bacilli retain their characteristics despite long residence in the human throat or transfer from one human being to another.

2. Avirulent diphtheria bacilli are devoid of pathogenic importance for man.

3. The carrier of avirulent diphtheria bacilli does not constitute a menace to the health of the community.

A CLINICAL METHOD FOR THE QUANTITATIVE DETERMINATION OF CALCIUM AND MAGNESIUM IN SMALL AMOUNTS OF SERUM OR PLASMA

By Benjamin Kramer and Frederick F. Tisdall

(From the Department of Pediatrics, The Johns Hopkins University, Baltimore)

The McCrudden method for the quantitative determination of calcium and magnesium in biological material[1] is considered the most reliable procedure for this purpose. The material to be analyzed is ashed and then dissolved in dilute hydrochloric acid. The solution is heated to boiling and the calcium precipitated by adding an excess of oxalic acid to the acid solution. It is then cooled and the acidity of the solution is diminished by the addition of a large amount of 20 per cent sodium acetate, thereby neutralizing the mineral acid and replacing it with a buffer solution of free acetic acid and sodium acetate in which calcium oxalate is practically insoluble. In the original description of the method the final determination is made by ashing the calcium oxalate until it is completely converted into calcium oxide. The latter is then weighed. The oxalate may, however, be titrated directly by means of acid potassium permanganate.

The latter procedure is to be preferred when determining calcium in small amounts of blood, serum or plasma, since one is here dealing with quantities of calcium too small to be weighed accurately. Under these conditions the amount of calcium oxalate has also been determined colorimetrically or by means of the nephelometer. Of such methods several have been reported. Most of these have been discussed elsewhere and hence will not be reviewed here.[2] All have one disadvantage in common, namely that the protein of the serum must either be removed by a preliminary precipitation or the organic matter destroyed by ashing.

We have succeeded in precipitating calcium and magnesium quantitatively from unashed serum by means of a modified McCrudden technique. This precipitation is the basis of the methods described below for the quantitative estimation of these elements in serum or plasma.

The Sample to be Analyzed

The method may be applied to serum or plasma. If sodium citrate in 0.9 per cent sodium chloride be used to prevent clotting, its final concentration in the blood should not exceed 1.5 per cent. Samples showing moderate or marked hemolysis cannot be used.* Although we have obtained good results

* The addition of oxalic acid or ammonium oxalate to a very dilute solution of ferric chloride yields a precipitate which is only slightly soluble even in glacial acetic acid.

To determine the calcium content of hemolyzed serum, dilute 2 c. c. of serum with 2 c. c. of water, then add 1 c. c. of 30 per cent ammonium acetate. After one hour make the volume up to 6 c. c. Centrifuge for 15 minutes, syphon off the supernatant fluid. Use 5 c. c. of this and proceed as for non-hemolyzed serum or plasma. Since the calcium determination is performed on 5/6 of 2 c. c. of serum, the proper correction should be made in the final calculation.

with several sera analyzed at intervals over a period of two weeks, it is preferable that the determination be done within 24 hours. Blood may be obtained by venipuncture or by the Blackfan method.[3] The clotted blood is centrifuged and the serum poured or pipetted off.

The Calcium Method

One or two cubic centimeters of serum or plasma are measured into an ordinary 15 c. c. graduated centrifuge tube containing from 2 to 3 c. c. of distilled water. The tube should be gently agitated after the addition of each drop of serum. Two drops of .01 per cent phenolsulphonphthalein are added followed by 1 drop of n/1 sulphuric acid. One drop of 30 per cent ammonium chloride is then added followed by 1 c. c. of approximately n/1 oxalic acid. The sample should be shaken after each addition.* One-half of 1 c. c. of a saturated solution of sodium acetate is added and the tube allowed to stand for at least one hour. The pH of the sample at this point is about 5.4 (di-brom-cresol). The sample is then made up to a definite volume, preferably 6 c. c., and centrifuged for at least 20 minutes at 1300 revolutions per minute. All but 0.2 c. c. or 0.3 c. c. of the supernatant fluid is syphoned off through a glass tube, the lower end of which is drawn out to a bore of about 1 mm. and curved so that the opening is directed upward. The lower opening in this tube should be at least 3 or 4 mm. above the precipitate. The precipitate is suspended in the residual liquid by stirring with a glass rod. Enough 2 per cent ammonia (2 c. c. of concentrated ammonia diluted to 100 c. c.) is then added to bring the volume to 4 c. c., care being taken to wash the rod and the sides of the centrifuge tube free from adherent oxalic acid. The tube is then centrifuged for 10 minutes. This procedure is repeated twice, thus making three washings in all. After the third washing the supernatant fluid is syphoned off, the tube is shaken to suspend the precipitate. 2 c. c. of approximately n/1 sulphuric acid are added and the tube is warmed in the boiling water-bath for a few minutes and titrated with n/100 potassium permanganate until a definite pink color persists for at least 1 minute when viewed under a good light against a white background. The strength of the permanganate solution is determined by titrating against an n/100 sodium oxalate (Sörensen).

Calculation.—The number of cubic centimeters of n/100 potassium permanganate used diminished by 0.02 c. c. (the blank) times 0.2 equals the mgms. of calcium in the sample. If 2 c. c. of serum are used, this figure multiplied by 50 equals the number of mgms. per 100 c. c. of serum. Thus, if the titration is 1.02 c. c. of n/100 potassium permanganate then $(1.02-.02)\times 0.2\times 50=10$ mgms. calcium per 100 c. c. serum.

Preparation of Reagents.—n/100 sodium oxalate (Sörensen). This is the only reagent that must be quantitatively accurate. An n/10 sodium oxalate (Sörensen) is prepared in the usual way. Six and seventh-tenths grams of sodium oxalate (Sörensen) are dissolved in water. Solution is facilitated by the addition of 5 c. c. of concentrated sulphuric acid and the volume made up to 1 liter. This is diluted ten times to make an n/100 solution. The former solution will keep indefinitely while the latter has been found still unchanged after the lapse of two months.

Approximately n/1 oxalic acid is prepared by dissolving 63 grams of oxalic acid (Kahlbaum or J. T. Baker, C. P.—calcium free) in a liter of water. The acid need be weighed only roughly.

Approximately n/1 Sulphuric Acid.—Fifty cubic centimeters of concentrated sulphuric acid (C. P.) are diluted with water to 1 liter.

Thirty Per Cent Ammonium Chloride.—Approximately 30.0 grams of ammonium chloride are dissolved in 100 c. c. of water. A sample of this should be diluted, an excess of ammonium oxalate solution added and the solution allowed to stand in order to rule out the presence of calcium.

Saturated sodium acetate solution is made by adding an excess of the salt to water and allowing it to stand over night. The supernatant fluid is then filtered.

Sodium acetate (J. T. Baker, C. P.) does not contain calcium.

PROTOCOLS

(1) Samples containing 0.236 mgm. of calcium as $CaCl_2$, .041 mgm. of magnesium as $MgSO_4$ and 0.615 mgm. of phosphorus as KH_2PO_4, were treated as above described for the calcium determination except that no oxalic acid was added. No precipitate appeared at the end of 24 hours. The pH of this solution was about 6.0—6.2 (di-brom-cresol). This indicates that neither calcium phosphate nor NH_4MgPO_4 is precipitated at this pH under the given conditions.

(2) Similar samples without calcium were treated as described in the method. Here again no precipitate appeared, indicating that magnesium oxalate remains in solution under these conditions.

(3) Solutions containing known amounts of calcium, magnesium and either potassium or sodium phosphate in concentrations corresponding to the maximum which we have found in serum were analyzed. The results given in Table I show that quantities of calcium varying from 0.096 mgm. to 0.386 mgm. can be recovered with a maximum error of 5 per cent.

(4) Known amounts of calcium were added to sera in which the calcium content had already been determined. The added calcium was quantitatively recovered (Table II).

(5) A series of parallel determinations on the sera of humans and animals was made by this method and by the method of Kramer and Howland. The results given in Table III show a satisfactory agreement between the two methods.

DISCUSSION

The investigations of Richards[4] and his collaborators have defined the necessary conditions for a quantitative separation of calcium from magnesium and for the exact gravimetric estimation of the former. The dangers in this procedure lie

* The precipitate which forms on the addition of ammonium chloride disappears on adding oxalic acid.

in the possible occlusion of undissociated magnesium oxalate in the calcium oxalate precipitate when precipitation occurs in a neutral solution in the presence of a large excess of highly ionized ammonium oxalate. The degree of occlusion varies with the concentration of undissociated magnesium oxalate.

In a solution of an electrolyte an equilibrium exists, as represented by the Mass law, betwen the undissociated magnesium oxalate and the free magnesium and oxalate ions, thus:

$$\frac{\overset{++}{Mg} \times \overset{=}{C_2O_4}}{MgC_2O_4} = K = \text{a constant.}$$

The maximum concentration of free magnesium and oxalate ions is determined by the solubility product constant of this salt.[5] This is the product of the ionic concentration of these two ions in a saturated solution of the salt at a given temperature. Thus, if the molar concentration of magnesium oxalate in a saturated solution is .0027 gm. mol. per liter, then if this is 80 per cent dissociated we have the concentration of $\overset{++}{Mg}$ = .0022 gm. mol. and that of oxalate = .0022 gm. mol., and the solubility product would then be .0000484 or 4.8×10^{-5} gm. mols. per liter.

The addition of a solution which contains a greater concentration of oxalate ions to a saturated solution of magnesium oxalate would so increase the concentration of this ion as to exceed the solubility product constant.[5] The concentration of free magnesium ions is therefore decreased through the formation of more undissociated magnesium oxalate. But the solution is already saturated as regards molecular magnesium oxalate, hence the excess of undissociated magnesium oxalate precipitates. The concentration of magnesium in serum is too small for even a great excess of oxalate ion to bring about precipitation but such an excess can so increase the concentration of molecular magnesium oxalate as to favor its occlusion by calcium oxalate.[6] The dilution of the serum and the addition of a mineral acid counteracts this tendency, the former by decreasing the concentration of both ions, per unit volume, the latter by decreasing that of the free oxalate ion, an effect to be attributed to the large excess of $\overset{+}{H}$ ions which the mineral acid contributes, thereby repressing the ionization of oxalic acid.[6] The mineral acid also keeps calcium phosphate in solution by forming the more soluble acid calcium phosphate ($CaHPO_4$).

McCrudden[3] has shown that in the separation of calcium from solutions containing this element along with magnesium and phosphates the precipitate of calcium oxalate may be contaminated with phosphates, presumably ammonium magnesium phosphate or tertiary calcium phosphate, unless the solution is sufficiently acid during precipitation. The required H-ion concentration is not stated. The proper degree of acidity for complete precipitation of pure calcium oxalate can be best obtained by the addition of a concentrated solution of sodium acetate. We have found that solutions whose pH's vary from 5.2–6.6 will permit complete precipitation of calcium oxalate if sufficient excess of oxalate ions be present.

CONCLUSIONS

I. A method has been described by means of which calcium may be determined directly in 2 c. c. of serum or plasma with a maximum error of ± 5 per cent.

II. No special apparatus is required, except an accurately calibrated 2 c. c. pipette and a micro-burette graduated in 1/50 of a c. c.

III. A determination may be completed within 2 hours after the sample of blood is obtained.

IV. The sources of error in the determination of calcium in small quantities of biological fluids have been discussed.

V. Comparative studies using this rapid method and the method of Kramer and Howland have shown that the former method yields results that agree well with those obtained by the latter.

The Magnesium Method

In 1871 Pribram[7] precipitated completely calcium as calcium oxalate and magnesium as ammonium magnesium phosphate from 100 c. c. samples of serum which had been previously rendered alkaline with ammonia, without preliminary destruction of the organic matter. Gerlach and E. Drechsel[8] stated that this precipitate contains phosphates unless precipitation is accomplished in acid solution. McCrudden[3] demonstrated that fairly accurate results can be obtained when magnesium is precipitated in the filtrate from the calcium determination without oxidation of the organic substances with nitric acid. We have obtained excellent results when omitting this step. Marriott and Howland[9] described a method for the determination of magnesium in small quantities of serum. The essential features of this method are first, the oxidation of the organic matter in the filtrate derived from the calcium determination, second, the precipitation of magnesium as NH_4MgPO_4 by the addition of $(NH_4)_2HPO_4$ and concentrated ammonia, third, the separation of the NH_4MgPO_4 from the supernatant fluid by centrifuging and washing five times, and fourth, the comparison of the degree of decolorization of a solution of $Fe(SCN)_3$ with the decolorization produced by a known amount of NH_4MgPO_4. We have simplified this method by eliminating the first step entirely, by using only one-fifth the amount of $(NH_4)_2HPO_4$, and by filtering the precipitate through a Gooch crucible and washing thoroughly. The colorimetric determination was not changed. The results obtained by the procedure as outlined above are more constant than those obtained by the method of Marriott and Howland.

PREPARATION OF REAGENTS

(1) *Ammonium Magnesium Phosphate Standard.*—This solution is made by dissolving 0.102 gm. of air-dried magnesium ammonium phosphate ($MgNH_4PO_4.6H_2O$) in 100 c. c. of 0.1 N hydrochloric acid and diluting to 1 liter with water. Of this solution 1 c. c. is equivalent to 0.01 mg. of magnesium. Magnesium ammonium phosphate loses water of crystallization when heated and must therefore be dried at room temperature. Commercial preparations of the salt are generally

unreliable; it should be prepared by precipitation of pure solutions. (See Jones, W., J. Biol. Chem., 1916, XXV, 87.)

(2) *Ammonium phosphate solution* is made as follows: 25 gm. $(NH_4)_2HPO_4$ are dissolved in 250 c. c. H_2O. 25 c. c. of concentrated ammonia are added and the mixture is allowed to stand over night. The following day it is filtered, the filtrate is boiled to remove the excess of ammonia, cooled, and made up to 250 c. c. This solution is diluted 5 times with water.

(3) The *ferric thiocyanate solution* is made from two solutions which are mixed an hour before use. Solution A is 0.3 per cent ammonium thiocyanate. Solution B is 0.3 per cent ferric chloride, made up from the salt with its contained water of crystallization, adding a few drops of acid, if necessary, to clear the solution. Five cubic centimeter portions of Solutions A and B are mixed and the whole is diluted to 40 c. c. with water.

(4) *10% Ammonia.*—One hundred cubic centimeters of concentrated ammonia is diluted to one liter.

THE METHOD

Five cubic centimeters of the supernatant fluid from the calcium determination corresponding to 1.66 c. c. serum is measured into a 30 c. c. beaker, 1 c. c. of $(NH_4)_2HPO_4$ solution is added and then 2 c. c. of concentrated ammonia. Next day the sample is filtered through a well packed Gooch crucible, washed ten times with 5 c. c. of 10 parts of concentrated ammonia to 90 parts of water, then twice with alcohol 95 per cent made alkaline with ammonia. The crucible is returned to the beaker and dried for a few minutes at 80° C. in the oven.

Ten cubic centimeters of n/100 HCl are added to the crucible and after a few hours the entire material is transferred to a test tube, centrifuged, and 5 c. c. of the supernatant fluid is measured into a flat-bottomed colorimeter tube graduated for 10 c. c., which contains 2 c. c. of the iron thiocyanate solution. The volume is then made up to 10 c. c. with n/100 HCl, a rubber stopper inserted and the fluid mixed. A series of standards is prepared by adding varying amounts of a known NH_4MgPO_4 solution to the thiocyanate solution and bringing the volume up to 10 c. c. as in the unknown samples. The color is compared by looking through the entire length of the liquid column against a white background.

Calculation.—The calculation is the same as in the orginal method: Reading (c. c. of standard solution) $\times .01 \times 2 \times 6/5 \times 50 =$ mgms. magnesium in 100 c. c. serum when 2 c. c. of serum are used.

PROTOCOLS

(1) A solution containing an amount of Mg per c. c. as the sulphate corresponding to the amount found in 2 c. c. of serum was analyzed. Magnesium was recovered quantitatively (Table V).

(2) Samples containing Ca, Mg and P in concentrations equal to those found in serum were analyzed both for Mg and Ca and both elements recovered within 5 per cent of the quantity actually present, Table VI.

(3) Magnesium added to serum was quantitatively recovered (Table VII).

(4) A series of determinations on normal adults, normal children, and children suffering from various diseases yielded results that agree well with those found by Marriott and Howland using the more elaborate procedure (Table IV).

CONCLUSIONS

A simplified method for the quantitative determination of magnesium in small quantities of serum or plasma has been described.

TABLE I.—ANALYSES OF SAMPLES OF SOLUTION B

	Calcium	
Spec. No.	Found mg.	Present mg.
1.....	0.093	....
2.....	0.093	....
3.....	0.096	....
4.....	0.092	....
Average...	0.094	0.096
5.....	0.186	....
6.....	9.193	....
7.....	0.193	....
8.....	0.182	....
Average...	0.188	0.192
9.....	0.383	....
10.....	0.375	....
11.....	0.385	....
12.....	0.381	....
Average...	0.381	0.386

NOTE:

Composition of Solution B

NaCl	4.634 gm.
KH_2PO_4	0.039
$MgSO_4$	0.758
$CaCO_3$	0.241
HCl conc.	10.0 c. c.
H_2O to	500 c. c.

TABLE II.—RECOVERY OF CALCIUM ADDED TO SERUM
Authors' Method

	Calcium			
Spec. No.	In serum	Added	Total found	Total present
	mg.	*mg.*	*mg.*	*mg.*
1	0.187	0.096	0.286	0.283
2	0.169	0.236	0.408	0.405
3	0.200	0.236	0.434	0.436
4	0.194	0.236	0.430	0.436

TABLE III.—COMPARATIVE DETERMINATIONS ON SERUM

	Methods	
Spec. No.	Method of Kramer and Howland	Authors' method
1	10.5	10.6
2	10.5	10.5
3	10.6	10.4
4	10.8	10.2

TABLE IV.—CALCIUM AND MAGNESIUM DETERMINATIONS IN NORMAL AND PATHOLOGICAL SERA

Spec. No.	Age	Sex	Diagnosis	Authors' method	
				Calcium per 100 c. c. serum	Magnesium per 100 c. c. serum
				mg.	*mg.*
1	Adult.	Male.	Normal.....	9.5	2.7
2	"	"	"	10.6	2.9
3	"	"	"	10.3	2.9
4	"	"	"	10.4	...
5	"	"	"	9.2	2.1
6	Sheep.	...	.....	9.5	2.1
7	"	...	.....	10.0	2.1
8	"	...	.....	10.4	1.9
9	17 yrs.	Male.	Osteogenesis imperfecta.	12.1	1.8
10	8 mos.	"	Tetany	5.5	1.6
11	8 mos.	"	Tetany (after $CaCl_2$).	7.6	1.8
12	2 yrs.	"	Rickets.....	9.2	2.3
13	8 mos.	"	"	7.7	2.2
14	3 yrs.	"	"	7.2	1.8
15	2½ yrs.	Female.	"	9.5	...
16	11 yrs.	Male.	Normal...	10.2	2.8
17	8 mos.	Female.	Scurvy	10.6	2.2

TABLE V.—ANALYSIS OF SAMPLES OF A SOLUTION OF MAGNESIUM SULPHATE

Spec. No.	Magnesium	
	Present	Found
	mg.	*mg.*
1	0.044	0.046
2	0.088	0.092
3	0.044	0.044
4	0.044	0.042

TABLE VI.—ANALYSIS OF 1 C. C. SAMPLES OF A SOLUTION CONTAINING Ca = 0.236 Mg. Mg = 0.041 Mg. P = 0.62 Mg.

Calcium		Magnesium	
Found	Present	Found	Present
0.230	0.236	0.043	0.044
0.233	....	0.040	....
0.230	....	0.041	....
0.244	....	0.046	....

TABLE VII.—RECOVERY OF MAGNESIUM ADDED TO SERUM

Magnesium			
Present	Added	Total found	Total present
mg.	*mg.*	*mg.*	*mg.*
0.038	0.044	0.080	0.082
0.044	0.088	0.137	0.132
0.044	0.044	0.086	0.088
0.042	0.044	0.089	0.086

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THE SURGICAL TREATMENT OF RHINOPHYMA, WITH REPORT OF A CASE

By EDWARD M. HANRAHAN, JR.

(From the Surgical Department of The Johns Hopkins Hospital)

Two papers on the surgical treatment of rhinophyma have appeared in the current year. Seelig in Surgery, Gynecology and Obstetrics, of April 1920, gave an account of a procedure by which he secured an excellent result. His operation consisted in the excision of the tumor mass and allowing healing to take place by epithelialization proceeding from niduses of epithelium which were left after the main part of the growth had been removed. He states that in the shaving off of the redundant tissue one should bear in mind two things, (1) not to shave so deeply as to remove all niduses of epithelium, and (2) to preserve a thin rim of epithelium around the nares to prevent cicatrization at this point by scar tissue. Bleeding in his case was controlled by pressure. Healing, that is, epithelialization, took place under imbricated strips of sterile zinc oxide adhesive plaster and was complete in ten days. Skin grafting was not found necessary.

Grattan in the Journal of the American Medical Association, May 22, 1920, describes an operation the basis of which is the utilization of skin flaps made by two U-shaped incisions over the tumor. The skin was dissected from the tumor, the mass dissected from the nasal structure and the flaps adapted to the new contour. Healing in his case occurred *per primam* and this patient left the hospital on the 10th day. The problem of improving the appearance of the flaps was met by the application of trichloracetic acid until the higher prominences of the skin were levelled. Roentgen rays were also used subsequently and the result as shown by his illustrations was most satisfactory.

A case of rhinophyma was lately operated on in this clinic by Dr. Mont R. Reid. The technique used was similar to that of Seelig in so far as the entire mass, including the skin, was excised, but differed in that a Thiersch graft was used to cover the denuded surface.

REPORT OF THE CASE

T. M., a white man, aged 42, was admitted to the hospital on October 8, 1919. The family history was negative. His past history was interesting in the fact that the patient had been troubled with acne vulgaris of the face since boyhood and that he gave also an unusual history of furunculosis. The patient had used alcohol in moderation between the ages of 20 and 40. He had also used chewing tobacco and snuff immoderately.

The first manifestation of the present condition had begun three years before admission during the latter part of 1916. At that time the patient had noticed that his nose was increasing in size. This enlargement had started on the left and spread gradually over the tip of the nose, finally involving the right side. The growth had been very gradual, almost imperceptible, painless and without obstruction to breathing. The patient now sought relief only because of the unsightliness of his appearance. The physical examination was negative except for the condition of the nose and skin. There was a bulbous enlargement of the nose the size of an English walnut, which involved both alæ and the tip. The skin was red, pitted and greasy to the touch. The mass felt firm, not œdematous nor fluctuant. The skin was closely attached to the underlying tumor mass. There was a small wart on the right ala.

The skin of the chest, back and particularly of the forearms was covered with small white scars and comedones. The patient said that the latter became affected only after doing work in which the arms became spattered with oil during the last two years, and that the onset of nasal enlargement had preceded this other condition.

The *Wassermann* was negative. The blood count was practically normal. The blood pressure was 162/105. The urine contained a trace of albumin and a few granular casts. S. G. 1018-1027.

Operation.—October 11, 1919. The nose was sterilized with alcohol. The hypertrophic skin was entirely cut away, healthy skin being left above the line of incision and a border of skin about the nares, about one-eighth of an inch wide. The base was then carefully curetted in order to remove all epithelium, care being taken not to injure the perichondrium. Bleeding was controlled by pressure, hot saline solution and adrenalin, a few catgut 00 ligatures being used on the large vessels. A Thiersch skin graft taken from the thigh was then applied to the denuded area, and a silver foil dressing placed over it. It should be noted that the manipulation during the removal of the tumor expressed large plugs of sebaceous material upon the operative field.

Post-Operative Care.—The recovery was complicated by a short attack of acute tonsillitis during the second week. The nose was dressed on the fifth day. Generally speaking the graft was in good condition except in two small areas on either ala, the larger on the right being about as large as one's little finger-nail. The nose was now kept moist and clean with Dakin's solution applied on compresses moistened every two hours. Healing was complete by the fourteenth day.

Microscopic Study of Excised Tissue.—There is thickening of both layers of the skin—particularly in the stratum corium. There are many papillary downgrowths of epidermis, particularly in the stratum germinativum, with areas of keratinization. The corium is extensively infiltrated with small round cells and shows a great increase of fibrous connective tissue. The ducts of the sebaceous glands are dilated and are lined with thickened epidermis. The glands are dilated and hypertrophied. The corium measures about 1 cm. in thickness and is of the same character throughout as described above. The thickened squamous epithelium of the ducts is present deep in the corium.

The microscopic pathology of this condition was fully described by Wende and Bentz in 1904. They noted the cystic enlargement of the sebaceous glands due to dilatation and hypertrophy of the excretory duct, the connective-tissue hypertrophy and round-cell infiltration and also the hypertrophy and cellular infiltration of the superficial layer of the epidermis. They described the stratum mucosum (germinatum) as thickened, with proliferation of some of the edges.

From a study of the microscopical sections it would seem that the disease is a mild chronic inflammatory reaction brought about by the accumulation of large quantities of sebum in dilated and hypertrophied glands. This inflammatory reaction manifests itself by hypertrophy of connective tissue and

round-cell infiltration in the corium and to a lesser extent is seen in the epidermis—particularly in the germinativum. This being the case, it would seem that the most logical procedure would be the removal of this diseased tissue in it's entirety. This is the method employed by Warren and White, and advocated by Seelig and Gibbon who remove all but small niduses of epithelium from which epithelialization proceeds. Grattan leaves only the outer layer of the skin, relying on his dissection of the skin from the deeper layers to remove all sebaceous gland tissue. It was noted, however, by Dubreuilh that in partial excision of slices and union by suture of the remaining portion the latter usually continued to grow and to produce more hypertrophic tissue.

Reid attempts to remove all diseased tissue, even the niduses of epithelium, with the idea of avoiding the development of retention cysts; and then relies on grafts to cover the defect. Either Reid's method or that of Seelig may be followed safely. The graft of healthy skin appears to be a more logical procedure than the use of flaps of skin which should not be considered healthy, and if one fears any injury to the nasal cartilage due to curetting too deeply, the healing from niduses of epithelium offers a very satisfactory result.

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EXPLANATION OF PLATES

FIGS. 1, 2.—Case of Rhinophyma. Duration of growth three years. Patient's age is 42. Acne vulgaris since boyhood.

FIGS. 3, 4.—Ten (10) days after operation. The Thiersch graft has taken.

FIGS. 5, 6.—Photograph forwarded by the patient four months after operation.

FIG. 7.—Photomicrograph magnified 18 times, showing a large dilated duct lined with squamous epithelium. At × a small nidus of epithelium could be left, and from such points the wound may be epithelialized.

FIG. 8.—Photomicrograph magnified 36 times, round-cell infiltration and overgrowth of fibrous connective tissue are apparent. The hypertrophied glands connecting with obstructed and dilated duct are well shown.

THE ISOLATION OF *B. DYSENTERIÆ* (FLEXNER) FROM THE URINE OF AN INFANT WITH DYSENTERY

By CATHERINE CREIGHTON, C. E. WAGNER AND WILBURT C. DAVISON

(From the Harriet Lane Home of The Johns Hopkins Hospital and the Department of Pediatrics of The Johns Hopkins University, Baltimore, Maryland)

True dysentery bacilli have rarely been found in the urine of patients suffering from dysentery.[1] Fraenkel[2] in a large series of urine cultures in adult cases of dysentery recovered dysentery bacilli in only four instances. In one of these patients *B. typhosus* as well as the dysentery bacillus was recovered from the urine. Hilgers[3] among a total of 82 cases of pyelocystitis found *B. dysenteriæ* in the urine of two patients, the first one being a man with chronic prostatitis and the other a child suffering from enteritis follicularis. Foerster[4] isolated *B. dysenteriæ* in another case of pyelocystitis. Sonne[5] found dysentery bacilli in the urine of a patient convalescent from typhoid fever. The organisms recovered in all of these cases were mannite-fermenting dysentery bacilli of the Flexner group. Organisms resembling but not identical with *B. dysenteriæ* have occasionally been isolated from the urine of individuals with other diseases.[6] Hæmorrhagic vaginitis[7] has also been noted as a complication of dysentery.

Our case illustrates that a typical *B. dysenteriæ* (Flexner) (Tables I and II) may be found in the catheterized urine of a child with bacillary dysentery without vaginitis, pyelitis, cystitis or other urinary complication. The organism was discovered as the result of routine cultures.

CASE REPORT

Female, white, No. 23721, aged 27 months. The onset of diarrhœa was rather gradual. The temperature reached 103° F. and there were from ten to fifteen bloody stools on the third day, passed with pain. After one week the patient began to improve and was admitted to this hospital on the fourteenth day of the disease with the complaint of persistent abdominal pain and dysuria. There were two to three bloody stools a day. All the symptoms subsided two days later.

The *physical examination* was essentially negative; there was no microscopic vaginal discharge.

Laboratory Findings.—W. B. C. 10,400; microscopic examination of a centrifuged specimen of uncatheterized urine on the sixteenth day of the disease showed pus cells in clumps (probably from the vagina), but no pus cells were found in catheterized specimens on the sixteenth and nineteenth days. *B. dysenteriæ* (Flexner) was isolated in pure culture from both of these latter specimens. Three weeks later the catheterized urine was sterile. Stool cultures on admission and on the three following days as well as three weeks later were negative for *B. dysenteriæ*. The absence of dysentery bacilli in the stools does not invalidate the diagnosis of bacillary dysentery, for

FIG. 4.

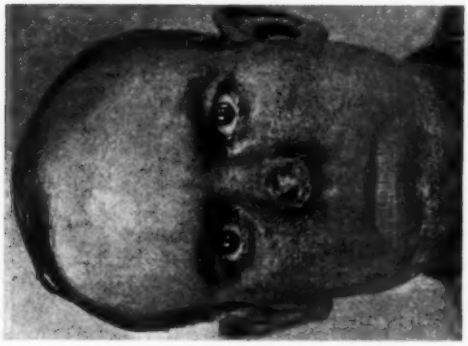

FIG. 3.

FIG. 2.

FIG. 1.

FIG. 5.

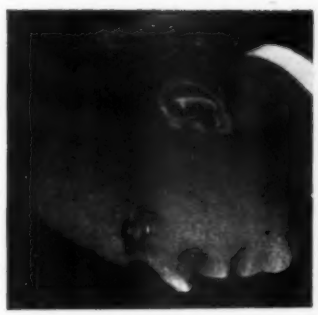

FIG. 6.

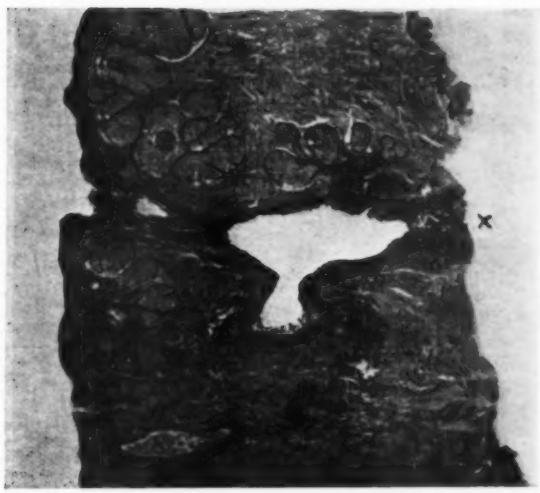

FIG. 7.

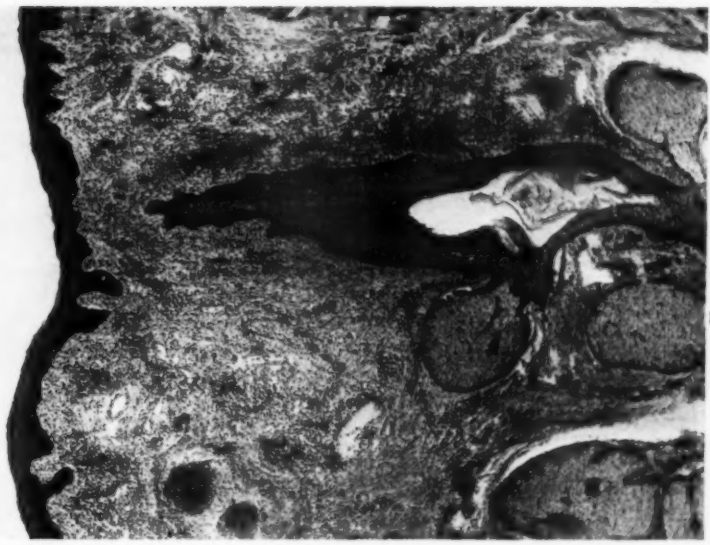

FIG. 8.

stool cultures are frequently negative at this late stage of the disease.

Blood culture one week after admission was sterile.

The agglutination reactions of the patient's serum with cultures of the dysentery bacillus isolated from her urine and also with stock cultures of *B. dysenteriæ* (Flexner) were positive on the seventeenth and thirty-eighth days of the disease (Table III).

Diagnosis.—Bacillary (Flexner) dysentery.

TABLE I.—BIOLOGICAL CHARACTERS OF THE DYSENTERY BACILLUS ISOLATED FROM THE PATIENT'S URINE

Gram stain	Motility	Indol	Gelatin	Lactose	Dextrose	Mannite	Maltose	Saccharose	Dulcite	Rhamnose	Xylose
0	0	0	0	0	+	+	+ (4th) (day)	0	0	0	0

0 indicates negative Gram-staining; non-motility; non-formation of indol (8 days); non-liquefaction of gelatin (28 days); non-fermentation of carbohydrate media (28 days).

+ indicates production of acid without gas in carbohydrate media. For cultural and serological technique, see reference.[5]

TABLE II.—AGGLUTINATION REACTIONS OF THE DYSENTERY BACILLUS ISOLATED FROM THE PATIENT'S URINE

Polyvalent dysentery serum (Rockefeller Institute)	Shiga serum	Polyvalent Flexner serum (Rockefeller Institute)	Flexner diagnostic type sera (Murray)[9]				
			V	W	X	Y	Z
+ 1250	0 100	+ 1000	0 100	+ 252	0 100	+ 250	0 100

+ in Tables II and III indicates complete agglutination at the dilution (end-point) noted after the sign.

0 indicates no agglutination at the dilution noted after the sign.

TABLE III.—AGGLUTINATION REACTIONS OF THE PATIENT'S SERUM

Day of the disease	Cultures of dysentery bacillus isolated from patient's urine	Formolized standard stock cultures					
		B. dysenteriæ (Shiga)	B. dysenteriæ (Flexner) Murray's Types[9]				
			V	W	X	Y	Z
17	+ 100	0 20	+ 20	+ 20	0 20	+ 200	+ 20
38	+ 50	0 20	+ 100	+ 50	0 20	+ 200	+ 20

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A CONTRIBUTION TO THE STAINING OF PHAGOCYTES AND EXUDATES

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The object of this communication is to place on record the formula of a stain which has been used in this laboratory throughout the last year for the study of phagocytosis and exudates. The preparation and application of this stain are so simple and rapid, the results so uniformly successful, that it seems generally a more satisfactory stain than those commonly used for staining phagocytic preparations. In composition the stain is somewhat similar to the one originally employed by Pappenheim[1] for staining plasma cells. The stain described in this paper, however, has been preferred because with it the nuclei and bacteria are more sharply and constantly stained, annoying precipitates are generally absent, while the uniformly shaded cytoplasm makes possible a clear definition of the cell configuration, and permits a rapid and accurate enumeration of even the smaller and most irregular organisms.

[1] Pappenheim, Arch. f. path. Anat., Berl., 1899, 157, 19-76.

Preparation of Stain.—The following solution is made up using neutral distilled water:

Distilled water (neutral)	100 c. c.
Glycerine	20 c. c.
Alcohol 95%	20 c. c.
Phenol	2 c. c.

To this is then added:

Crystal violet	0.060 gr.
Pyronin	0.200 gr.

The flask is agitated to insure complete solution. This requires not more than two or three minutes. The stain is not filtered and is ready for immediate use. It may be preserved indefinitely if direct sunlight is avoided and the container is kept tightly closed to prevent evaporation of the alcohol.

Method of Using.—The smears of the material to be examined are made upon well cleaned glassware and allowed

to dry in the air. Any further fixation is only an unnecessary addition to the technique without any compensatory advantage. Smears prepared in this manner stick well and if the slides are slightly warmed before the smears are applied it is often possible to preserve the ameboid form of the cells. The slide is then flooded with the stain and after five to ten seconds is thoroughly washed in a jet of distilled water. As direct blotting often injures the cells, it has been found desirable to withdraw the water that may adhere to the smear by touching the side of the slide with a blotter. Stains made in this fashion have been kept in the laboratory for eight months without any marked alterations in the appearance of the preparations.

The best results are possible only when the slides are thoroughly cleaned. It is quite impossible to make a satisfactory smear upon an unclean slide. The presence of grease and other foreign substance presents a precipitating focus which often makes it necessary to discard the smear altogether. Stitt's suggestion of passing the slide slowly through a flame to remove grease and lint before making the smear has proved exceedingly valuable.

Stains made with the above technique present about the following appearance. The cell nuclei are stained violet, the cytoplasm a uniformly delicate lavender. Often a reticular structure can be made out in the extranuclear substance but granules are never present to interfere with the bacterial enumeration. The cell limits are clearly and sharply defined. The bacteria are colored a deep purple and can readily be distinguished from detached nuclear material that may resemble them morphologically. When, however, the intracellular organisms are being digested they gradually lose their staining qualities, appearing as shadowed outlines, and finally disappear leaving only a vacuole filled with granules. Bacteria such as gonococci, which vigorously resist digestion, retain their staining characteristics for days after being ingested. Erythrocytes, when present, appear as pale lavender shadows. Plasma and mast cells exhibit a characteristic structure and stain darkly throughout, so they are at once recognized. Unformed albuminous and mucoid extracellular constituents of exudates seem to possess little affinity for the stain so that the field appears quite clear. There is a total absence of the annoying precipitates too often associated with the staining of phagocytes.

The above stain has also been used as a routine in this laboratory for the preliminary examination of exudates. Its sharp bacterial staining qualities together with the slight affinity of the stain for the extracellular material make possible the demonstration of organisms even when they are present only in exceedingly small numbers. The use of this stain has been found most advantageous in exudates where an excess of cellular debris and serum produce precipitation with resulting confusion when the more common bacterial stains are used. The exact demarcation of cell outlines enables one to determine at a glance the presence of intracellular organisms.

A CLINICAL STUDY OF TUBERCULOUS SALPINGITIS,* BASED UPON 200 CASES

By J. P. GREENBERG

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Tuberculosis of the female reproductive organs was formerly considered a very rare condition. Up till the time that Hegar's monumental monograph appeared in 1886 tuberculosis of the female productive organs had been looked upon as a rarity. After the appearance of Hegar's communication, interest in the subject was aroused and since then an enormous literature has appeared. The actual incidence of the disease is still underrated, and there is little wonder that many cases are overlooked when we stop to reflect that the diagnosis is in the majority of cases made only after careful microscopical examination. As recently as 1909 the disease was considered uncommon enough to justify the reports in the literature of individual uncomplicated cases.

In discussing tuberculosis of the tubes, we are really considering the large majority of the cases of tuberculosis of the genital tract, for in nearly all the latter cases the tubes are involved. Furthermore, in a discourse on tuberculous salpingitis we must of necessity make constant reference to tuberculous peritonitis, for the two cannot be separated.

Incidence.—We have analysed all the cases of tuberculous salpingitis which have occurred on the Gynecological service of The Johns Hopkins Hospital during the last 30 years, (1890-1919 inclusive). In this report we shall give a clinical study of those cases only which showed definitely, upon microscopic examination, that tuberculosis was present. Fulfilling this requirement we found exactly 200 cases. This, of course does not give the actual morbidity of the disease; for many patients having tuberculous peritonitis with tubal involvement did not have their tubes removed. We had 67 such patients; and if we agree with Osler and Menge that about 35% of these patients have tuberculous salpingitis, we find that among the 67 patients, 23 had tubal tuberculosis. Hence instead of 200 cases of tuberculous salpingitis we have had in all probability 223. Our clinical study, however, is based only on the 200 cases in which the tubes were without doubt tuberculous.

During the 30 years there have been 24,155 patients suffering from gynecological disorders. The incidence of tuberculous salpingitis therefore is 0.83%, or considering the number of patients as 223, we find that the incidence is 0.92%.

Incidence of Tuberculous Salpingitis Compared with All Diseases of the Tubes.—During the last 30 years there have

* The complete article, of which this is an abstract, will appear in The Johns Hopkins Hospital Reports.

FIG. 1.—Illustrating the appearance of phagocytes and bacteria in smears prepared according to the technique described in this paper. (A) Pus cell from a lung abscess in a multiple infection. (B) Polymorphonuclear leucocyte from the blood of a guinea pig twenty-five minutes after the ingestion of B. proteus. The bacteria are surrounded by vacuoles. One bacillus, partially digested, has lost its staining characteristics. The cell is associated with erythrocytes. (C) Smear from a lung abscess containing cocci, bacilli, and spirochetes. (D) Polymorphonuclear leucocyte containing a colon bacillus within a digestive vacuole.

been 3382 salpingectomies at The Johns Hopkins Hospital. Of this number, in 423 the tubes proved to be normal. There remained then 2959 cases in which the tubes were pathological. Since there were in this period of time 200 cases of tubal tuberculosis, the incidence of tuberculous salpingitis as compared with the abnormal tubes is 6.76%. This figure however does not give us the actual incidence. We must take into consideration the 23 cases before mentioned, in which there was peritoneal tuberculosis but in which the diagnosis of tubal tuberculosis was not verified because the tubes were not removed. Considering therefore 223 cases, we find that of the 2959 pathological tubes, 7.5% were tuberculous, a figure that more nearly approximates the truth. This means that out of every 13 abnormal tubes removed, one was tuberculous.

Age.—Our youngest patient was 14 years old; while the oldest was 55. The greater number (73.5%) were in the child-bearing period (between 20-40 years).

Fertility.—In our series there were 159 (79.5%) married and 41 (20.5%) unmarried women. Of the former, 101 (63.5%) had never been pregnant, and since about 90% of them had been married at least two years, which may be accepted as a reasonable period for the determination of the sterility or fertility of a married woman, we may assume that about 60% of our patients were actually sterile. Of the 41 single women, six had been pregnant (14.6%).

Symptoms.—The various symptoms are considered in full in the complete report. We shall here briefly refer only to those of major importance.

On admission to the hospital, more than 80% of the patients complained of pain in the lower abdomen, and about 30% had concomitant pain in the back. Pain around the umbilicus, which is so often quoted as being characteristic of tuberculous peritonitis, was elicited in only 7%, although, as will be pointed out, 63% of the patients had peritoneal tuberculosis.

The following menstrual disturbances were noted; dysmenorrhea (62%), menorrhagia (41.5%), oligomenorrhea (24%) and amenorrhea (6.5%).

Among the 200 patients, 72% had a leukorrheal discharge and all the patients with tuberculosis of the cervix had leukorrhea.

Predisposing Causes.—An appreciable number of patients attributed the onset of their infection to some special uterine activity. Seventy-four patients gave a history of a definite onset, and of this number 46 or 62.2% (23% of the 200 patients), dated their trouble from some uterine function or disturbance, as may be seen from the following table:

Time of onset		No.		%	
Menstrual period	Uterine Activity	22	46	11.0%	23%
Childbirth		15		7.5	
Miscarriage		6		3.0	
Pregnancy		2		1.0	
Induced abortion		1		0.5	
Marriage		9		4.5	
Acute illness		9		4.5	
Operation		4		2.0	
Injury		4		2.0	
Menopause		1		0.5	
Fright		1		0.5	
		74		37.0%	

Physical Examination.—For the complete data bearing on the physical examination, the reader is referred to the more extensive article. Mention may here be made, however, of the more important findings.

Pulmonary tuberculosis occurred in about one-fourth, and tenderness in the lower abdomen was elicited in about three-fourths of the patients. Of interest in the pelvic examination was the fact that although 7 patients had tuberculosis of the cervix, the condition was recognized only once. In 70%, masses were found in the fornices, replacing the normal adnexa.

Elevation of Temperature.—Considering a temperature of 99.2° or above as fever, we found that 125 of our 200 patients (62.5%) had a pre-operative elevation of temperature. Among the patients having peritoneal involvement, 65.8% had pre-operative fever, while of those having apparently no peritoneal involvement, it occurred in only 34.2%.

Leukocyte Count.—The leukocyte count was recorded 50 times. Only 34% of these patients had a count of more than 9000, while 22% had an absolute leukopenia. Whereas the remainder apparently had a normal count (between 6000-9000), they in reality had a relative leukopenia. For most of them had fever at the time the count was made and in conditions other than tuberculosis a definite leukocytosis should have been found.

Hemoglobin.—In 62 patients the hemoglobin was determined by the Sahli method. If we consider 70% as the lower normal limit, we find that 50% of these patients presented too low a hemoglobin.

Pre-Operative Diagnosis.—No diagnosis was recorded before operation in 34 instances. The correct diagnosis was made before operation in only 26 instances (13%). However, 15 of these patients had ascites which made the diagnosis an easy one. The most frequent diagnosis was "Pelvic Inflammatory Disease," by which was meant in practically all instances, a gonorrheal or puerperal affection. Myomata were diagnosed 29 times and were actually found associated with tuberculosis in 25 cases.

Treatment.—All the cases but two which are here reported were operative cases and in every instance the operation was performed by the abdominal route. In 10 patients this was combined with pelvic puncture. A radical operation was performed 106 times (53%). The uterus was removed in 124 cases (62%), while there were 166 oöphorectomies (83%), unilateral or bilateral. Salpingectomy alone was performed 18 times (9%). Exploratory laparotomy was done in five cases, in all of which the autopsy showed tuberculous tubes.

Drainage.—Among our 200 cases 104 (52%) were drained. Recourse was had to abdominal drainage in 28 instances (14%), to vaginal drainage 58 times (29%) and to combined abdominal and pelvic drainage in 18 cases (9%). In the 104 patients who had been drained, there were 18 fecal fistulæ, an incidence of 17.3%. None of the 96 patients who were not drained developed a fecal fistula.

Order of Frequency of Organs Involved.—The order of frequency of involvement of the various pelvic organs in the tuberculous process is as follows:

Tubes	200
Uterus	90
Ovaries	59
Cervix	7
Vagina	1

Tuberculosis of the Uterus.—The uterus was involved 90 times (45%). If we seek the incidence of uterine tuberculosis among the hysterectomies, we find it to be 72.6%. This figure more nearly represents the actual occurrence of tuberculosis of the uterus. The following table shows the distribution of the disease process in the uterus:

Endometrium	86
Myometrium	12
Endometrium alone	78
Myometrium alone	4
Endometrium and myometrium	8

As may be seen, tuberculosis limited to the myometrium is rare. Of the 86 patients with tuberculous endometritis, all but three were in the menstruating age and among them amenorrhea occurred in only 7 (8.4%); menorrhagia in 37.2%.

Tuberculosis of the Ovary.—The ovaries were found to be tuberculous 55 times; hence the incidence based upon the number of oöphorectomies (166) was 33.1%.

Tuberculosis of the Cervix.—In our 200 cases of tubal tuberculosis, the cervix was involved seven times (3.5). In addition to these, two other cases of tuberculosis of the cervix were noted but not associated with tuberculosis of the tubes.

Among the cervical cases associated with tubal tuberculosis other portions of the uterus were involved as follows:

Cervix and endometrium together	3
Cervix, endometrium and myometrium	3
Cervix alone	1

Tuberculosis of the Vagina.—Vaginal tuberculosis was found in only one case (0.5%).

Tuberculosis of the Peritoneum and Appendix.—Peritoneal tuberculosis was found in 126 of the 200 patients (63%). In most of our cases the appendix was removed. We found six cases of tuberculosis, making our incidence at least 3%.

Combinations of Organs Involved.—The following list indicates the manner in which the various organs were associated together in the disease.

Tubes involved alone	37	18.5%
Tubes and peritoneum	49	24.5
Tubes and uterus	23	11.5
Tubes, uterus and peritoneum	33	16.5
Tubes and ovaries	3	1.5
Tubes, ovaries and peritoneum	19	9.5
Tubes, uterus and ovaries	8	4.0
Tubes, uterus, ovaries and peritoneum	20	10.0
Tubes, ovaries and cervix	1	0.5
Tubes, ovaries, uterus and cervix	1	0.5
Tubes, uterus and cervix	1	0.5
Tubes, uterus, cervix and peritoneum	1	0.5
Tubes, uterus, ovaries, cervix and peritoneum	3	1.5
Tubes, uterus and vagina	1	0.5
	200	100.0%

Deaths in the Hospital.—In our 200 cases there were 17 deaths in the hospital (8.5%). Of this number, however, only 15 of the patients had been operated upon; hence the operative mortality in 198 cases was 7.6%.

Of the 17 patients who died, 7 had definite signs of pulmonary tuberculosis on physical examination, while in 3 others the diagnosis was questionable. Or, considered differently, 9 of our 58 patients with definite or suspicious phthisis died immediately after operation (15.5%), as compared with 7 (5%) in 142 patients without pulmonary involvement.

Out of our 125 patients with an elevation of temperature, there was 14 deaths (11.2%), while in the 75 patients without fever, there were only three deaths (4%).

In the 126 patients with peritoneal involvement, the operative mortality was 11.1%; in the 74 patients without peritoneal tuberculosis the mortality was only 2.7%.

It appears, therefore, that the prognosis is graver when there is tuberculosis elsewhere, when a pre-operative elevation of temperature exists, and when the peritoneum is involved in the tuberculous process.

Late Results.—An effort was made to communicate with the 183 patients who were discharged from the hospital, but unfortunately information could be obtained only regarding ninety (66 white and 24 colored women). To draw conclusions from these is not only hazardous but is also erroneous, as only half the patients are represented. However, the results are interesting.

Of the 90 patients, 12 had died; but 3 deaths had had no relation to the tuberculosis. (One after a gall-bladder operation, one after an automobile accident and the third following an operation for carcinoma of the abdominal wall.)

Among the 78 living patients who responded, the general health had markedly improved after operation in 73, somewhat in 2 and not at all in 3. There had been a gain in weight in 73 patients, which in many instances was very marked. The pain had been absolutely relieved in 72, partly in 4 and not at all in 2. Eleven patients complained of bladder disturbances. Ten patients who were discharged from the hospital with open wounds, reported that the wounds had subsequently closed, at intervals varying from 2 weeks to 2 years. In 3 patients the wound, which was healed at the time of discharge from the hospital, reopened, but closed again spontaneously. Post-operative hernia occurred in 7 patients.

CONCLUSIONS

We may summarize the findings of our 200 cases of tuberculous salpingitis as follows:

1. Tuberculous salpingitis occurred in nearly 1% of all women admitted on the gynecological service of The Johns Hopkins Hospital.

2. It was found one and a half times as frequently among the colored women as among the white.

3. Out of every 13 abnormal tubes removed at operation, one was tuberculous.

4. Nearly three-fourth of the patients were between 20 and 40 years of age.

5. Sixty per cent of the married patients were sterile.

6. A family history of tuberculosis was reported in 22.5%, while in an additional 2.5% the consort had active pulmonary tuberculosis.

7. The chief complaint of the patient was pain (74.5%) usually situated in the lower abdomen (82.5%).

8. Not much information was obtained from the menstrual history. However, 62% of the patients had dysmenorrhea and 41.5% menorrhagia. Amenorrhea occurred in only 6.5% of the patients.

9. Leukorrhea occurred in 72% of the patients.

10. Nearly half of the patients had dysuria, nycturia and pollakiuria.

11. More than half of the patients were constipated.

12. Approximately one-fourth of the patients attributed the onset of their symptoms to some uterine activity (menstruation, pregnancy, etc.).

13. Half of the patients had lost weight during their illness.

14. The physical examination presented no characteristic findings.

15. About one-fourth of the patients had pulmonary tuberculosis.

16. Pre-operative elevation of temperature was recorded in 62.5%.

17. There was usually either an absolute or a relative leukopenia.

18. Half of the patients examined had a hemoglobin below normal limits.

19. The correct diagnosis before operation was made in only 13% of the cases and, in more than half of these, the diagnosis was aided by the presence of ascites.

20. A radical operation was performed in 53% of the cases.

21. Complications during operation occurred in 14.5% of the patients.

22. One hundred and four cases were drained. Of these, 17.3% developed fecal fistulæ. Abdominal fecal fistulæ occurred 3 times more frequently among the cases drained abdominally than in those drained through the vagina.

23. In one-third of all the patients, there was suppuration of the abdominal incision.

24. No patients who were not drained, developed a fecal fistula.

25. The incidence of fecal fistulæ among the cases in which the bowel had been injured was 48%, whereas among the cases in which the intestines had remained intact, the incidence was only 3.4%. The patients with pre-operative fever developed fecal fistulæ more than twice as frequently as those without fever.

26. Urinary fistulæ occurred 5 times (2.5%).

27. The order of frequency of involvement of the pelvic organs was as follows: tubes, uterus, ovaries, cervix and vagina. Tuberculosis of these organs was found associated with tubal tuberculosis as follows: uterus, 72.6%; ovaries, 33.1%; cervix, 3.5%; and vagina, 0.5%.

28. In 99% of the cases both tubes were involved.

29. In 68% of the cases the peritoneum was involved, and in 3% the appendix was tuberculous.

30. In 17% myomata uteri were associated with the tuberculous process.

31. In only 2% was there an associated involvement of the urinary tract.

32. The prognosis is grave in the presence of tuberculosis elsewhere in the body, where fever exists and where the peritoneum is involved.

33. Our operative mortality was 7.6%. (This includes all the patients who died in the hospital.)

34. By means of follow-up letters, etc., 90 patients were traced and out of this number, 78 were found to be living from 2 months to 30 years after the operations. Nearly all those who are alive are in good condition.

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